09/583,310 Search Strategy/Results

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     (FILE 'HOME' ENTERED AT 15:08:07 ON 21 FEB 2002)

     FILE 'MEDLINE, AGRICOLA, CAPLUS, BIOSIS, EMBASE, WPIDS' ENTERED AT
     15:08:16 ON 21 FEB 2002
L1         65212 S MONOOXYGENASE
L2           111 S L1 AND (TYPE (W) (3 OR III))
L3            16 S L2 AND LIVER
L4             6 S L3 AND HUMAN
L5             3 DUP REM L4 (3 DUPLICATES REMOVED)
L6           561 S FMO3 OR FMOS OR FMO-3 OR FMO-III
L7           561 S FMO3 OR FMOS OR FMO-3 OR FMO-III OR FMOIII
L8           243 S L7 AND HUMAN AND LIVER
L9           243 S L7 AND (HUMAN OR SAPIENS) AND LIVER
L10           62 S L9 AND (DNA OR POLYNUCLEOTIDE OR NUCLEIC OR NUCLEOTIDE)
L11          124 S L9 AND (DNA OR POLYNUCLEOTIDE OR NUCLEIC OR NUCLEOTIDE OR RN
L12          125 S L9 AND (DNA OR POLYNUCLEOTIDE OR NUCLEIC OR NUCLEOTIDE OR RN
L13           42 DUP REM L12 (83 DUPLICATES REMOVED)

     FILE 'CAPLUS' ENTERED AT 15:17:04 ON 21 FEB 2002
                E CASHMAN L/AU 25
                E CASHMAN J/AU 25
L14           48 S (E3 OR E6 OR E13 OR E15 OR E16) AND (MONOOXYGENASE AND LIVER)
L15           20 S (E3 OR E6 OR E13 OR E15 OR E16) AND (MONOOXYGENASE AND LIVER
                E LOMRI N/AU 25
L16            5 S (E3 OR E4 OR E5 OR E6 OR E7) AND (MONOOXYGENASE AND LIVER AND

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CONTINUE? Y/(N):y

L13 ANSWER 1 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002045707 EMBASE
TITLE: Cloning, sequencing, and tissue-dependent expression of flavin-containing monooxygenase (FMO) 1 and **FMO3** in the dog.
AUTHOR: Lattard V.; Longin-Sauvageon C.; Lachuer J.; Delatour P.; Benoit E.
CORPORATE SOURCE: Dr. E. Benoit, Unite de Toxicologie, UMR INRA et DGER, Ecole Nationale Veterinaire de Lyon, BP 83, 69280 Marcy l'etoile, France. e.benoit@vet-lyon.fr
SOURCE: Drug Metabolism and Disposition, (2002) 30/2 (119-128). Refs: 33
ISSN: 0090-9556 CODEN: DMDSAI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The expression of flavin-containing monooxygenases (**FMOs**) in dog **liver** microsomes was suggested by a high methimazole S-oxidase activity. When the reaction was catalyzed by dog **liver** microsomes, apparent V(max) and K(m) values were 6.3 nmol/min/mg and 14 .mu.M, respectively. This reaction was highly inhibited (73%) in the presence of imipramine, but it was also weakly affected by trimethylamine, suggesting the involvement of different isoforms. The sequences of dog FMO1 and **FMO3** were obtained by reverse transcription-polymerase chain reaction and 5'/3' terminal extension. The cDNAs of dog FMO1 and dog **FMO3** encode proteins of 532 amino acids, which contain the NADPH- and FAD-binding sites. The dog FMO1 amino acid sequence is 88, 86, and 89% identical to sequences of **human**, rabbit, and pig FMO1, respectively. The dog **FMO3** amino acid sequence is 83, 84, and 82% identical to sequences of **human**, rabbit, and rat **FMO3**, respectively. Dog FMO1 and dog **FMO3** exhibited only 56% identities. The FMO1 and **FMO3** recombinant proteins and the FMO1 and **FMO3** microsomal proteins migrated with the same mobility (56 kDa), as determined in SDS-polyacrylamide gel electrophoresis and immunoblotting. By Western blotting, dog FMO1 and dog **FMO3** were detected in microsomes from **liver** and lung but not in kidney microsomes. By Northern blotting, the probe for FMO1 specifically hybridized a 2.6-kilobase (kb) transcript in **liver** and lung samples only. The probe for **FMO3** hybridized two transcripts of approximately 3 and 4.2 kb in the **liver** and lung samples.

L13 ANSWER 2 OF 42 MEDLINE
ACCESSION NUMBER: 2001677283 MEDLINE
DOCUMENT NUMBER: 21580262 PubMed ID: 11723251
TITLE: Regulation of flavin-containing monooxygenase 1 expression by ying yang 1 and hepatic nuclear factors 1 and 4.
AUTHOR: Luo Z; Hines R N
CORPORATE SOURCE: Departments of Pediatrics and Pharmacology and Toxicology, Birth Defects Research Center, Medical College of Wisconsin, Milwaukee, Wisconsin 53226-4801, USA.
CONTRACT NUMBER: CA53106 (NCI)
SOURCE: MOLECULAR PHARMACOLOGY, (2001 Dec) 60 (6) 1421-30. Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF355464
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011128
Last Updated on STN: 20020123
Entered Medline: 20011221
AB The flavin-containing monooxygenases (**FMOs**) are important for the oxidation of a variety of environmental toxicants, natural products, and therapeutics. Consisting of six family members (FMO1-5), these enzymes exhibit distinct but broad and overlapping substrate specificity and are expressed in a highly tissue- and species-selective manner. Corresponding to previously identified regulatory domains, a YY1 binding site was identified at the major rabbit FMO1 promoter, position -8 to -2, two overlapping HNF1alpha sites, position -132 to -105, and two HNF4alpha sites, position -467 to -454 and -195 to -182. Cotransfection studies with HNF1alpha and HNF4alpha expression vectors demonstrated a major role for each of these factors in enhancing FMO1 promoter activity. In contrast, YY1 was shown by site-directed mutagenesis to be dispensable for basal

promoter activity but suppressed the ability of the upstream domains to enhance transcription. Finally, comparisons between rabbit and **human** FMO1 demonstrated conservation of each of these regulatory elements. With the exception of the most distal HNF4alpha site, each of the orthologous **human** sequences also was able to compete with rabbit FMO1 cis-elements for specific protein binding. These data are consistent with these same elements being important for regulating **human** FMO1 developmental- and tissue-specific expression.

L13 ANSWER 3 OF 42 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001679458 IN-PROCESS
DOCUMENT NUMBER: 21582395 PubMed ID: 11725960
TITLE: Identification of **human** drug-metabolizing enzymes involved in the metabolism of SNI-2011.
AUTHOR: Washio T; Arisawa H; Kohsaka K; Yasuda H
CORPORATE SOURCE: Research Institute of Life Science, Snow Brand Milk Products Co, Ltd, Shimotsuga-gun, Tochigi, Japan.. washio-t-e@pop16.odn.ne.jp
SOURCE: BIOLOGICAL AND PHARMACEUTICAL BULLETIN, (2001 Nov) 24 (11) 1263-6.
Journal code: 9311984. ISSN: 0918-6158.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20020123

AB In vitro studies were conducted to identify **human** drug-metabolizing enzymes involved in the metabolism of SNI-2011 ((+/-)-cis-2-methylspiro [1,3-oxathiolane-5,3'-quinuclidine] monohydrochloride hemihydrate, cevimeline hydrochloride hydrate). When 14C-SNI-2011 was incubated with **human liver** microsomes, SNI-2011 trans-sulfoxide and cis-sulfoxide were detected as major metabolites. These oxidations required NADPH, and were markedly inhibited by SKF-525A, indicating that cytochrome P450 (CYP) was involved. In a chemical inhibition study, metabolism of SNI-2011 in **liver** microsomes was inhibited (35-65%) by CYP3A4 inhibitors (ketoconazole and troleandomycin) and CYP2D6 inhibitors (quinidine and chlorpromazine). Furthermore, using microsomes containing **cDNA**-expressed CYPs, it was found that high rates of sulfoxidation activities were observed with CYP2D6 and CYP3A4. On the other hand, when 14C-SNI-2011 was incubated with **human** kidney microsomes, SNI-2011 N-oxide was identified as a major metabolite. This N-oxidation required NADPH, and was completely inhibited by thiourea, indicating that flavin-containing monooxygenase (FMO) was involved. In addition, microsomes containing **cDNA** -expressed FMO1, a major isoform in **human** kidney, mainly catalyzed N-oxidation of SNI-2011, but microsomes containing **FMO3** , a major isoform in adult **human liver**, did not. These results suggest that SNI-2011 is mainly catalyzed to sulfoxides and N-oxide by CYP2D6/3A4 in **liver** and FMOI in kidney, respectively.

L13 ANSWER 4 OF 42 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001501077 MEDLINE
DOCUMENT NUMBER: 21435636 PubMed ID: 11551524
TITLE: Quantification and cellular localization of expression in **human** skin of genes encoding flavin-containing monooxygenases and cytochromes P450.
AUTHOR: Janmohamed A; Dolphin C T; Phillips I R; Shephard E A
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University College London, London, UK.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (2001 Sep 15) 62 (6) 777-86.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010912
Last Updated on STN: 20010924
Entered Medline: 20010920

AB The expression, in adult **human** skin, of genes encoding flavin-containing monooxygenases (**FMOs**) 1, 3, 4, and 5 and cytochromes P450 (CYPs) 2A6, 2B6, and 3A4 was determined by RNase protection. Each FMO and CYP exhibits inter-individual variation in expression in this organ. Of the individuals analysed, all contained CYP2B6 **mRNA** in their skin, 90% contained FMO5 **mRNA** and about half contained mRNAs encoding **FMOs** 1, 3, and 4, and CYPs 2A6 and 3A4. The amount of each of the FMO and CYP mRNAs in skin is much

lower than in the organ in which it is most highly expressed, namely the kidney (for FMO1) and the **liver** (for the others). In contrast to the latter organs, in the skin FMO mRNAs are present in amounts similar to, or greater than, CYP mRNAs. Only the **mRNA** encoding CYP2B6 decreased in abundance in skin with increasing age of the individual. All of the mRNAs were substantially less abundant in cultures of keratinocytes than in samples of skin from which the cells were derived. In contrast, an immortalized **human** keratinocyte cell line, HaCaT, expressed **FMO3**, FMO5, and CYP2B6 mRNAs in amounts that fall within the range detected in the whole skin samples analysed. FMO1, CYP2A6, and CYP3A4 mRNAs were not detected in HaCaT cells, whereas FMO4 expression was markedly increased in this cell line compared to whole skin. In situ hybridization showed that the expression of each of the **FMOs** and CYPs analysed was localized to the epidermis, sebaceous glands and hair follicles.

L13 ANSWER 5 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:306993 BIOSIS
DOCUMENT NUMBER: PREV200100306993
TITLE: Over production of nitric oxide and peroxynitrite in patients with **liver** cirrhosis and cancer suppresses flavin-containing monooxygenase (FMO) activity and causes trimethylaminuria (TMAU.
AUTHOR(S): Yi, H. G.; Park, C. S.; Kang, J. S.; Kang, J. H.; Chung, W. G.; Pie, J. E.; Ryu, S. D.; Choi, W.; Cha, Y. N.
SOURCE: FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A576. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In 5 patients with **liver** cirrhosis and cancer, trimethylaminuria (TMAU) also known as Fish Odor Syndrome, a congenital metabolic disorder generally caused by gene defect in flavin-containing monooxygenase, is observed. In **human**, major part of **FMO3** is expressed in the **liver** and catalyzes the N-oxidation of volatile trimethylamine (TMA) derived from choline diets to non-volatile TMA N-oxide excreted in urine. Thus, when the hepatic **FMO3** activity is suppressed by hepatitis, cirrhosis and cancer, TMAU can be acquired. Prior to surgery, the in vivo FMO activities determined by urinary excretion of TMA N-oxide derived from normal diet were found to be low. Furthermore, the in vitro FMO activities (N-oxidation of ranitidine) determined with **liver** microsomes of patients similarly affected were found to be very low. Conversely, the plasma concentration of NO metabolites was increased by 3-6 fold of healthy volunteers. In the cirrhotic **liver** tissues obtained from patients after surgery, the contents of **FMO3 mRNA** and protein were very low and in the cancerous tissues, they were almost absent. In the cirrhotic and cancerous **liver** tissues, however, the expected over-expression of iNOS could not be clearly detected (immuno-histochemistry and Western-blot). **FMO3** present in the **human liver** microsomes obtained from these surgical tissues was found to be nitrated in Western-blot. This in vivo **FMO3** nitration result was confirmed in vitro by treating **human liver** microsomes obtained from normal **liver** with SIN-1, a donor of peroxynitrite (ONOO-). Combined, these results suggest that the over-produced NO and ONOO under a LPS-induced septic condition (Park et al., 1999) or a **liver** cirrhosis and cancer (present study) may cause TMAU both by suppression of FMO gene expression and by nitration of expressed FMO.

L13 ANSWER 6 OF 42 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001165255 MEDLINE
DOCUMENT NUMBER: 21163847 PubMed ID: 11266081
TITLE: A novel deletion in the flavin-containing monooxygenase gene (**FMO3**) in a Greek patient with trimethylaminuria.
AUTHOR: Forrest S M; Knight M; Akerman B R; Cashman J R; Treacy E P
CORPORATE SOURCE: Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia..
forrest@cryptic.rch.unimelb.edu.au
CONTRACT NUMBER: GM36426 (NIGMS)
SOURCE: PHARMACOGENETICS, (2001 Mar) 11 (2) 169-74.
Journal code: BRT; 9211735. ISSN: 0960-314X.
PUB. COUNTRY: England: United Kingdom

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB Mutations of the flavin-containing monooxygenase type 3 gene (**FMO3**) that encode the major functional form present in adult **human liver**, have been shown to cause trimethylaminuria. We now report a novel homozygous deletion of exons 1 and 2 in an Australian of Greek ancestry with TMAuria, the first report of a deletion causative of trimethylaminuria. The deletion occurs 328 bp upstream from exon 1. The 3'-end of the deletion occurs in intron 2, 10013 base pairs downstream from the end of exon 2. The deletion is 12226 bp long. For the proband homozygous for the **human FMO3** gene deletion, it is predicted that in addition to loss of monooxygenase function for **human FMO3** substrates, such as TMA and other amines, the proband will exhibit decreased tolerance of biogenic amines, both medicinal and those found in foods.

L13 ANSWER 7 OF 42 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001351709 MEDLINE
DOCUMENT NUMBER: 21308417 PubMed ID: 11414682
TITLE: Cloning, sequencing, tissue distribution, and heterologous expression of rat flavin-containing monooxygenase 3.
AUTHOR: Lattard V; Buronfosse T; Lachuer J; Longin-Sauvageon C; Moulin C; Benoit E
CORPORATE SOURCE: Unite de Toxicologie et de Metabolisme Compares des Xenobiotiques, UMR INRA et DGER, Ecole Nationale Veterinaire de Lyon, 69280 Marcy l'etoile, France.
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (2001 Jul 1) 391 (1) 30-40.
Journal code: 6SK; 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF286595
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB The sequence of rat **FMO3** was obtained by RT-PCR and 5'/3' terminal extension. Complete **cDNA** was amplified, cloned, and sequenced. The **cDNA** encodes a protein of 531 amino acids which contains the NADPH- and FAD-binding sites and a hydrophobic carboxyl terminus characteristic of **FMOs**. This sequence is 81, 81, and 91% identical to sequences of **human**, rabbit, and mouse **FMO3**, respectively, and 60% identical to rat FMO1. Rat **FMO3** was expressed in Escherichia coli. The recombinant protein and the native protein purified from rat **liver** microsomes migrated with the same mobility (56 kDa) as determined in sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immunoblotting. Recombinant rat **FMO3** showed activities of methimazole S-oxidation, and NADPH oxidation associated with the N- or S-oxidation of trimethylamine and thioacetamide, in good concordance with those reported for **human FMO3**. When probed with rat **FMO3 cDNA** (bases 201 to 768), a strong signal corresponding to the 2.3-kb **FMO3** transcript was detected in **RNA** samples from rat **liver** and kidney while a weak signal was observed with lung **RNA** samples. In contrast, the probe did not hybridize with any **RNA** from brain, adipose tissue, or muscle. Copyright 2001 Academic Press.

L13 ANSWER 8 OF 42 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001030942 MEDLINE
DOCUMENT NUMBER: 20493209 PubMed ID: 11038163
TITLE: In vitro evaluation of the disposition of A novel cysteine protease inhibitor.
AUTHOR: Jacobsen W; Christians U; Benet L Z
CORPORATE SOURCE: Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, California 94143-0446, USA.
CONTRACT NUMBER: CA72006 (NCI)
SOURCE: DRUG METABOLISM AND DISPOSITION, (2000 Nov) 28 (11) 1343-51.
Journal code: EBR. ISSN: 0090-9556.
PUB. COUNTRY: United States

(EVALUATION STUDIES)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001120

AB K11777 (N-methyl-piperazine-Phe-homoPhe-vinylsulfone-phenyl) is a potent, irreversible cysteine protease inhibitor. Its therapeutic targets are cruzain, a cysteine protease of the protozoan parasite Trypanosoma cruzi, and cathepsins B and L, which are associated with cancer progression. We evaluated the metabolism of K11777 by **human liver** microsomes, isolated cytochrome P450 (CYP) enzymes, and flavin-containing monooxygenase 3 (**FMO3**) in vitro. K11777 was metabolized by **human liver** microsomes to three major metabolites: N-oxide K11777 (apparent K(m) = 14.0 +/- 4.5 microM and apparent V(max) = 3460 +/- 3190 pmol. mg(-1). min(-1), n = 4), beta-hydroxy-homoPhe K11777 (K(m) = 16.8 +/- 3.5 microM and V(max) = 1260 +/- 1090 pmol. mg(-1). min(-1), n = 4), and N-desmethyl K11777 (K(m) = 18.3 +/- 7.0 microM and V(max) = 2070 +/- 1830 pmol. mg(-1). min(-1), n = 4). All three K11777 metabolites were formed by isolated CYP3A and their formation by **human liver** microsomes was inhibited by the CYP3A inhibitor cyclosporine (50 microM, 54-62% inhibition) and antibodies against **human** CYP3A4/5 (100 microg of antibodies/100 microg microsomal protein, 55-68% inhibition). CYP2D6 metabolized K11777 to its N-desmethyl metabolite with an apparent K(m) (9.2 +/- 1.4 microM) lower than for CYP3A4 (25.0 +/- 4.0 microM) and **human liver** microsomes. The apparent K(m) for N-oxide K11777 formation by **cDNA** -expressed **FMO3** was 109 +/- 11 microM. Based on the intrinsic formation clearances and the results of inhibition experiments (CYP2D6, 50 microM bufuralol; **FMO3** mediated, 100 mM methionine) using **human liver** microsomes, it was estimated that CYP3A contributes to >80% of K11777 metabolite formation. K11777 was a potent (IC(50) = 0.06 microM) and efficacious (maximum inhibition 85%) NADPH-dependent inhibitor of **human** CYP3A4 mediated 6'beta-hydroxy lovastatin formation, suggesting that K11777 is not only a substrate but also a mechanism-based inhibitor of CYP3A4.

L13 ANSWER 9 OF 42 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
ACCESSION NUMBER: 2000:614884 CAPLUS
DOCUMENT NUMBER: 133:290618
TITLE: Isoform specificity of N-deacetyl ketoconazole by **human** and rabbit flavin-containing monooxygenases
AUTHOR(S): Rodriguez, Rosita J.; Miranda, Cristobal L.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis, OR, 97331-3507, USA
SOURCE: Drug Metab. Dispos. (2000), 28(9), 1083-1086
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB N-Deacetyl ketoconazole (DAK) is the major metabolite of orally administered ketoconazole. This major metabolite has been demonstrated to be further metabolized predominately by the flavin-contg. monooxygenases (**FMOs**) to the secondary hydroxyl-amine, N-deacetyl-N-hydroxyketoconazole (N-hydroxy-DAK) by adult and postnatal rat hepatic microsomes. Our current investigation evaluated the FMO isoform specificity of DAK in a pyrophosphate buffer (pH 8.8) contg. the glucose 6-phosphate NADPH-generating system. **CDNA**-expressed **human FMOs** (FMO1, **FMO3**, and FMO5) and **cDNA**-expressed rabbit **FMOs** (FMO1, FMO2, **FMO3**, and FMO5) were used to assess the metab. of DAK to its subsequent FMO-mediated metabolites by HPLC anal. **Human** and rabbit **cDNA**-expressed **FMO3** resulted in extensive metab. of DAK in 1 h (71.2 and 64.5%, resp.) to N-hydroxy-DAK (48.2 and 47.7%, resp.) and two other metabolites, metabolite 1 (11.7 and 7.8%, resp.) and metabolite 3 (10.5 and 10.0%, resp.). Previous studies suggest that metabolite 1 is the nitrone formed after successive FMO-mediated metab. of N-hydroxy-DAK. Moreover, these studies display similar metabolic profiles seen with adult and postnatal rat hepatic microsomes. The **human** and rabbit FMO1 metabolized DAK pre-dominately to the N-hydroxy-DAK in 1 h (36.2 and 25.3%, resp.) with minimal metab. to the other metabolites (.ltoreq.5%). Rabbit FMO2 metabolized DAK to N-hydroxy-DAK (15.9%) and metabolite 1 (6.6%). Last, DAK did not appear to be a substrate for

human or rabbit FMO5. Heat inactivation of cDNA -expressed FMOs abolished DAK metabolite formation. These results suggest that DAK is a substrate for human and rabbit FMO1 and FMO3, rabbit FMO2, but not human or rabbit FMO5.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001017163 EMBASE
TITLE: Compound heterozygosity for missense mutations in the flavin-containing monooxygenase 3 (FMO3) gene in patients with fish-odour syndrome.
AUTHOR: Dolphin C.T.; Janmohamed A.; Smith R.L.; Shephard E.A.; Phillips I.R.
CORPORATE SOURCE: I.R. Phillips, Molecular and Cellular Biology, Division of Biomedical Sciences, Queen Mary and Westfield College, Mile End Road, London E1 4NS, United Kingdom. ir.phillips@qmw.ac.uk
SOURCE: Pharmacogenetics, (2000) 10/9 (799-807). Refs: 29 ISSN: 0960-314X CODEN: PHMCEE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Fish-odour syndrome is a highly unpleasant disorder of hepatic trimethylamine (TMA) metabolism characterized by a body odour reminiscent of rotting fish, due to excessive excretion of the malodorous free amine. Although fish-odour syndrome may exhibit as sequelae with other conditions (e.g. liver dysfunction), many patients exhibit an inherited, more persistent form of the disease. Ordinarily, dietary-derived TMA is oxidized to the non-odorous N-oxide by hepatic flavin-containing monooxygenase 3 (FMO3). Our previous demonstration that a mutation. P153L (C to T), in the FMO3 gene segregated with the disorder and inactivated the enzyme confirmed that defects in FMO3 underlie the inherited form of fish-odour syndrome. We have investigated the genetic basis of the disorder in two further affected pedigrees and report that the three propositi are all compound heterozygotes for causative mutations of FMO3. Two of these individuals possess the P153L (C to T) mutation and a novel mutation, N61S (A to G). The third is heterozygous for novel. M4341 (G to A), and previously reported. R492W (C to T), mutations. Functional characterization of the S61, 1434 and W492 variants, via baculovirus-mediated expression in insect cells, confirmed that all three mutations either abolished, or severely attenuated, the capacity of the enzyme to catalyse TMA N-oxidation. Although 1434 and W492 were also incapable of catalysing the S-oxidation of methimazole, S61 was fully active with this sulphur-containing substrate. Since an asparagine is conserved at the equivalent position to N61 of FMO3 in mammalian, yeast and Caenorhabditis elegans FMOs, the characterization of the naturally occurring N61S (A to G) mutation may have identified this asparagine as playing a critical role specifically in FMO-catalysed N-oxidation. .COPYRGT. 2000 Lippincott Williams & Wilkins.

L13 ANSWER 11 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:114393 BIOSIS
DOCUMENT NUMBER: PREV200100114393
TITLE: Sequence variation in the human flavin-containing monooxygenase 3 gene (FMO3): Identification by denaturing-high performance liquid chromatography (DHPLC.
AUTHOR(S): Charon, C. M. (1); Dolphin, C. T. (1)
CORPORATE SOURCE: (1) Department of Pharmacy, King's College London, Stamford Street, London, SE1 8WA UK
SOURCE: Biochemical Society Transactions, (October, 2000) Vol. 28, No. 5, pp. A435. print. Meeting Info.: 18th International Congress of Biochemistry and Molecular Biology Birmingham, UK July 16-20, 2000 ISSN: 0300-5127.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L13 ANSWER 12 OF 42 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000476205 MEDLINE
DOCUMENT NUMBER: 20477761 PubMed ID: 11026737

TITLE: Cytochrome P-450 enzymes and **FMO3** contribute to the disposition of the antipsychotic drug perazine in vitro.
AUTHOR: Stormer E; Brockmoller J; Roots I; Schmider J
CORPORATE SOURCE: Humboldt-University Berlin, Institute of Clinical Pharmacology, Germany.
SOURCE: PSYCHOPHARMACOLOGY, (2000 Sep) 151 (4) 312-20. Journal code: QGI. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB RATIONALE: Perazine (PER) is a phenothiazine antipsychotic drug frequently used in Germany that undergoes extensive metabolism. OBJECTIVES AND METHODS: To anticipate metabolic drug interactions and to explore the relevance of polymorphisms of metabolic enzymes, perazine-N-demethylation and perazine-N-oxidation were investigated in vitro using **human liver** microsomes and **cDNA** expressed enzymes. RESULTS: CYP3A4 and CYP2C9 were identified as the major enzymes mediating PER-N-demethylation. At 10 microM PER, a concentration consistent with anticipated in vivo **liver** concentrations, CYP3A4 and CYP2C9 contributed 50% and 35%, respectively, to PER-N-demethylation. With increasing PER concentrations, contribution of CYP2C9 decreased and CYP3A4 became more important. In **human liver** microsomes, PER-N-demethylation was inhibited by ketoconazole (>40%) and sulfaphenazole (16%). Allelic variants of recombinant CYP2C9 showed differences in PER-N-demethylase activity. The wild type allele CYP2C9*1 was the most active variant. Maximal activities of CYP2C9*2 and CYP2C9*3 were 88% and 18%, respectively, compared to the wild type activity. Perazine-N-oxidation was mainly mediated by **FMO3**. In the absence of NADPH, heat treatment of microsomes abolished PER-N-oxidase activity. Methimazole inhibited PER-N-oxidation, while CYP specific inhibitors had no inhibitory effect. Perazine is a potent inhibitor of dextromethorphan-O-demethylase, S-mephenytoin-hydroxylase, alprazolam-4-hydroxylase, phenacetin-O-deethylase and tolbutamide-hydroxylase activity in **human liver** microsomes. CONCLUSIONS: Alterations in the activity of CYP3A4, CYP2C9 and **FMO3** through genetic polymorphisms, enzyme induction or inhibition bear the potential to cause clinically significant changes in perazine clearance. PER may alter the clearance of coadministered compounds metabolized by CYP2D6, CYP2C19, CYP2C9, CYP3A4 and CYP1A2.

L13 ANSWER 13 OF 42 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000501240 MEDLINE
DOCUMENT NUMBER: 20500167 PubMed ID: 11048672
TITLE: The house musk shrew (Suncus murinus): a unique animal with extremely low level of expression of mRNAs for CYP3A and flavin-containing monooxygenase.
AUTHOR: Mushiroda T; Yokoi T; Itoh K; Nunoya K; Nakagawa T; Kubota M; Takahara E; Nagata O; Kato H; Kamataki T
CORPORATE SOURCE: Division of Pharmacobio-dynamics, Graduate School of Pharmaceutical Sciences, Hokkaido University, Japan.. mushiroda@hokuriku-seiyaku.co.jp
SOURCE: COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY. TOXICOLOGY & PHARMACOLOGY, (2000 Jul) 126 (3) 225-34. Journal code: DTU. ISSN: 1532-0456.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010201

AB Expression of drug-metabolizing enzymes including cytochrome P450 (CYP) and flavin-containing monooxygenase (FMO) in various tissues of Suncus murinus (Suncus) were examined. Northern blot analysis showed that mRNAs hybridizable with cDNAs for rat CYP1A2, **human** CYP2A6, rat CYP2B1, **human** CYP2C8, **human** CYP2D6, rat CYP2E1, **human** CYP3A4 and rat CYP4A1 were expressed in various tissues from Suncus. The **mRNA** level of CYP2A in the Suncus lung was very high. Furthermore, it was found that the level of CYP2A **mRNA** in the Suncus lung was higher compared to the Suncus **liver**. The expression level of **mRNA** hybridizable with **cDNA** for

human CYP3A4 was very low. The presence of CYP3A gene in Suncus was proven by the induction of the CYP with dexamethasone. Very low expression levels of mRNAs hybridizable with cDNAs for rat FMO1, rat FMO2, rat FMO3 and rat FMO5 were also seen in Suncus liver. No apparent hybridization band appeared when human FMO4 cDNA was used as a probe. The hepatic expression of mRNAs hybridizable with cDNAs for UDP-glucuronosyltransferase 1*6, aryl sulfotransferase, glutathione S-transferase 1, carboxyesterase and microsomal epoxide hydrolase in the Suncus were observed. These results indicate that the Suncus is a unique animal species in that mRNAs for CYP3A and FMO are expressed at very low levels.

L13 ANSWER 14 OF 42 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2000123346 MEDLINE
DOCUMENT NUMBER: 20123346 PubMed ID: 10659950
TITLE: Interspecies comparison and role of human cytochrome P450 and flavin-containing monooxygenase in hepatic metabolism of L-775,606, a potent 5-HT(1D) receptor agonist.
AUTHOR: Prueksaritanont T; Lu P; Gorham L; Sternfeld F; Vyas K P
CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA.. thomayant-prueksaritanont@merck.com
SOURCE: XENOBIOTICA, (2000 Jan) 30 (1) 47-59.
Journal code: XQU; 1306665. ISSN: 0049-8254.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000307

AB 1. Quantitative species differences and human liver enzymes involved in the metabolism of L-775,606, a potent and selective 5-HT1D receptor agonist developed for the acute treatment of migraine headache, have been investigated in vitro. 2. In human, monkey, dog and rat liver microsomes, formation of the hydroxylated M1 and the N-dealkylated M2 was mediated by enzyme(s) of high-affinity (apparent Km approximately 1-6 microM), and that of the two N-oxide isomers (M3) was catalysed by those of low affinity (apparent Km approximately 50-110 microM). In dog, M3 constituted a major pathway (approximately 40%), whereas in all other species it was a minor metabolite (< 5%). 3. In human liver microsomes, a marked inhibition (> or =80%) of M1 and M2 formation was observed by SKF525-A, troleandomycin, ketoconazole and anti-CYP3A antibodies, whereas the inhibition was modest (approximately 20-40%) with quercetin. Of seven cDNA-expressed human P450 tested, only CYP3A4 and CYP2C8 were capable of oxidizing L-775,606, resulting primarily in M1 and M2. However, CYP3A4 possessed much higher affinity (> or = 20-fold) and much higher intrinsic activity (> 100-fold) than CYP2C8. 4. In contrast, N-oxidation was not inhibited by any inhibitors of P450 tested, but rather was reduced significantly by heat treatment and methimazole, and was increased substantially with an incubation pH>7.4. Human flavin-containing monooxygenase form 3 (FMO3) catalysed exclusively the N-oxidation to M3, with apparent Km and optimum pH comparable with those observed in human liver microsomes. 5. These results demonstrated quantitative interspecies differences in the metabolism of L-775,606. In human, metabolism of L-775,606 to the principal metabolites, M1 and M2, was mediated primarily by CYP3A4 with minimal contribution from CYP2C8, whereas the minor N-oxidative pathway was catalysed mainly by FMO3.

L13 ANSWER 15 OF 42 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2000269720 MEDLINE
DOCUMENT NUMBER: 20269720 PubMed ID: 10807940
TITLE: Stereoselective sulfoxidation of sulindac sulfide by flavin-containing monooxygenases. Comparison of human liver and kidney microsomes and mammalian enzymes.
AUTHOR: Hamman M A; Haehner-Daniels B D; Wrighton S A; Rettie A E; Hall S D
CORPORATE SOURCE: Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN 46202, USA.
CONTRACT NUMBER: AG07631 (NIA)
GM43511 (NIGMS)
SOURCE: BIOCHEMICAL PHARMACOLOGY, (2000 Jul 1) 60 (1) 7-17.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20000629
Entered Medline: 20000616

AB The stereoselective sulfoxidation of the pharmacologically active metabolite of sulindac, sulindac sulfide, was characterized in **human liver**, kidney, and **cDNA**-expressed enzymes. Kinetic parameter estimates (pH = 7.4) for sulindac sulfoxide formation in **human liver** microsomes (N = 4) for R- and S-sulindac sulfoxide were V(max) = 1.5 +/- 0.50 nmol/min/mg, K(m) = 15 +/- 5.1 microM; and V(max) = 1.1 +/- 0.36 nmol/min/mg, K(m) = 16 +/- 6.1 microM, respectively. Kidney microsomes (N = 3) produced parameter estimates (pH = 7.4) of V(max) = 0.9 +/- 0.29 nmol/min/mg, K(m) = 15 +/- 2.9 microM; V(max) = 0.5 +/- 0.21 nmol/min/mg, K(m) = 22 +/- 1.9 microM for R- and S-sulindac sulfoxide, respectively. In **human liver** and flavin-containing monooxygenase 3 (**FMO3**) the V(max) for R-sulindac sulfoxide increased 60-70% at pH = 8.5, but for S-sulindac sulfoxide was unchanged. In fourteen **liver** microsomal preparations, significant correlations occurred between R-sulindac sulfoxide formation and either immunoquantified FMO or nicotine N-oxidation (r = 0.88 and 0.83; P < 0.01). The R- and S-sulindac sulfoxide formation rate also correlated significantly (r = 0.85 and 0.75; P < 0.01) with immunoquantified FMO in thirteen kidney microsomal samples. Mild heat deactivation of microsomes reduced activity by 30-60%, and a loss in stereoselectivity was observed. Methimazole was a potent and nonstereoselective inhibitor of sulfoxidation in **liver** and kidney microsomes. n-Octylamine and membrane solubilization with lubrol were potent and selective inhibitors of S-sulindac sulfoxide formation. **cDNA**-expressed CYPs failed to appreciably sulfoxidate sulindac sulfide, and CYP inhibitors were ineffective in suppressing catalytic activity. Purified mini-pig **liver** FMO1, rabbit lung FMO2, and **human cDNA**-expressed **FMO3** efficiently oxidized sulindac sulfide with a high degree of stereoselectivity towards the R-isomer, but FMO5 lacked catalytic activity. The biotransformation of the sulfide to the sulfoxide is catalyzed predominately by **FMOs** and may prove to be useful in characterizing FMO activity.

L13 ANSWER 16 OF 42 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1999268413 MEDLINE
DOCUMENT NUMBER: 99268413 PubMed ID: 10338091
TITLE: Two novel mutations of the **FMO3** gene in a proband with trimethylaminuria.
AUTHOR: Akerman B R; Forrest S; Chow L; Youil R; Knight M; Treacy E P
CORPORATE SOURCE: C.R. Scriver Biochemical Genetics Unit, Montreal Children's Hospital, Quebec, Canada.
SOURCE: HUMAN MUTATION, (1999) 13 (5) 376-9.
Journal code: BRD; 9215429. ISSN: 1059-7794.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U39960; GENBANK-U39961; GENBANK-U39962; GENBANK-U39963; GENBANK-U39964; GENBANK-U39965; GENBANK-U39966; GENBANK-U39967
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 19990820
Entered Medline: 19990811

AB The mammalian flavin-containing monooxygenases catalyze the NADPH-dependent N-oxygenation of nucleophilic nitrogen-, sulfur-, and phosphorus-containing chemicals, drugs, and xenobiotics, including trimethylamine. The **FMO3** gene encodes the dominant catalytically active isoform present in **human liver**. We have identified two missense mutations in the coding region of the gene in a proband with trimethylaminuria (TMA): M66I and R492W. Whereas two mutations (P153L, E305X) accounted for TMA in our eight unrelated previously documented Australian families of British origin, the present report is the first evidence of compound heterozygosity for two rare mutations in a proband with this disorder. This suggests that other rarer alleles, also causing TMA, will be found in the same populations.

L13 ANSWER 17 OF 42 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1999102145 MEDLINE

DOCUMENT NUMBER: 99102145 PubMed ID: 9884321
TITLE: In vitro metabolism of the M1-muscarinic agonist 5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine by **human** hepatic cytochromes P-450 determined at pH 7.4 and 8.5.
AUTHOR: Jensen K G; Dalgaard L
CORPORATE SOURCE: Department of Drug Metabolism, H. Lundbeck A/S, Ottiliavej 9, Copenhagen-Valby, Denmark.. KGJ@Lundbeck.com
SOURCE: DRUG METABOLISM AND DISPOSITION, (1999 Jan) 27 (1) 125-32. Journal code: EBR; 9421550. ISSN: 0090-9556.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990316
Last Updated on STN: 19990316
Entered Medline: 19990301

AB Biotransformation of the M1-muscarinic agonist Lu 25-109 (5-(2-ethyl-2H-tetrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine) , in development for the treatment of Alzheimer's disease, was investigated to obtain information on the identity of **human** hepatic cytochrome P-450 enzymes involved in its metabolism. The identification of these P-450s was accomplished through studies using 1) simple regression analysis with 14 phenotyped **human liver** samples, 2) selective chemical inhibitors, and 3) microsomes containing **cDNA** -expressed enzymes. The production of some metabolites is enhanced in vitro when the pH of the incubation media is shifted from pH 7.4 to 8.5. The metabolite production in **human liver** microsomes was NADPH-dependent, suggesting that the metabolism of Lu 25-109 in **human liver** microsomes is primarily P-450-dependent. Lu 25-109 was metabolized by **human liver** microsomes to Lu 31-126 (de-ethyl Lu 25-109) mainly by CYP2D6; to Lu 29-297 [3-(2-ethyltetrazol-5-yl)-1-methyl-pyridinium] and Lu 25-077 (demethyl Lu 25-109) mainly by CYP1A2, CYP2A6, CYP2C19, and CYP3A4; and to Lu 32-181 (Lu 25-109 N-oxide) by CYP1A2 and possibly by CYP2C19. One metabolite, Lu 32-181 (N-oxide), could be reduced back to Lu 25-109, a reaction not inhibited by the applied cytochrome P-450 inhibitors. This study did not indicate any involvement of **FMO3** or MAO in the in vitro metabolism of Lu 25-109 in **human liver** microsomes.

L13 ANSWER 18 OF 42 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97426128 MEDLINE
DOCUMENT NUMBER: 97426128 PubMed ID: 9282832
TITLE.: Detoxication of tyramine by the flavin-containing monooxygenase: stereoselective formation of the trans oxime.
AUTHOR: Lin J; Cashman J R
CORPORATE SOURCE: Seattle Biomedical Research Institute, Washington 98109, USA.
CONTRACT NUMBER: 00269 (NIDA)
DA 08531 (NIGMS)
GM 36426
+
SOURCE: CHEMICAL RESEARCH IN TOXICOLOGY, (1997 Aug) 10 (8) 842-52. Journal code: A5X; 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971013
Last Updated on STN: 19971013
Entered Medline: 19971001

AB In the presence of pig or adult **human liver** microsomes, tyramine was metabolized to the corresponding trans oxime through the intermediacy of the hydroxylamine. The requisite intermediate, (4-hydroxyphenethyl)hydroxylamine, was retroreduced to tyramine or converted stereoselectively to the trans oxime in the presence of pig or adult **human liver** microsomes. Studies of the effect of metabolic inhibitors suggested that formation of the trans oxime and retroreduction of the hydroxylamine were largely dependent on NADPH and the flavin-containing monooxygenase (FMO) and cytochrome P450, respectively. The conclusion that FMO was predominantly responsible for trans oxime formation in **human liver** microsomes was based on the effect of incubation conditions on tyramine N-oxygenation and the observation that **cDNA**-expressed **human FMO3** also N-oxygenated tyramine to give exclusively the trans oxime. The

synthetic hydroxylamine and oxime metabolites of tyramine were examined for affinity to **human** and animal dopamine and serotonin receptors and the **human** dopamine transporter. For all of the receptors and for the transporter examined, the avidity of the hydroxylamine and oximes was greater than 10 microM and beyond the effective concentration for physiological relevance. The results suggested that tyramine was sequentially N-oxygenated in the presence of pig and **human liver** microsomes and **cDNA**-expressed **FMO3** to the hydroxylamine and then to the di-N-hydroxylamine that was spontaneously dehydrated to the trans oxime. This may be facilitated by FMO through a nondissociative substrate-enzyme interaction. Based on the biogenic amine receptor or transporter affinity for the hydroxylamine and oxime metabolites of tyramine, N-oxygenation of tyramine by pig or **human liver** FMO may represent a detoxication reaction that terminates the pharmacological activity of tyramine.

L13 ANSWER 19 OF 42 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97227540 EMBASE
DOCUMENT NUMBER: 1997227540
TITLE: Baculovirus-mediated expression and purification of **human FMO3**: Catalytic, immunochemical, and structural characterization.
AUTHOR: Haining R.L.; Hunter A.P.; Sadeque A.J.M.; Philpot R.M.; Rettie A.E.
CORPORATE SOURCE: A.E. Rettie, Department of Medicinal Chemistry, Box 357610, University of Washington, Seattle, WA 98195, United States
SOURCE: Drug Metabolism and Disposition, (1997) 25/7 (790-797). Refs: 33
ISSN: 0090-9556 CODEN: DMDSAI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The baculovirus expression vector system was used to overexpress **human FMO3** in insect cells for catalytic, structural, and immunochemical studies. Membranes prepared from infected Trichoplusia ni cell suspensions catalyzed NADPH-dependent metabolism of methylp-tolyl sulfide at rates 20 times faster than those obtained with detergent-solubilized **human liver** microsomes. Sulfoxidation of the methyl and ethyl p-tolyl sulfides by recombinant **human FMO3** proceeded with little stereochemical preference, whereas sulfoxidation of the n-propyl and n-butyl homologs demonstrated increasing selectivity for formation of the (R)-sulfoxide. This chiral fingerprint recapitulated the metabolite profile obtained when detergent-treated **human liver** microsomes served as the enzyme source. Catalytically active **human FMO3** was purified to apparent homogeneity by cholate solubilization and sequential column chromatography on Octyl-Sepharose, DEAE-Sepharose, and hydroxyapatite. Purified **FMO3** exhibited the same electrophoretic mobility as native microsomal enzyme, and immunoquantitation showed that this isoform represents .apprx.0.5% of **human liver** microsomal protein. Therefore, **FMO3** is quantitatively a major **human liver** monooxygenase. LC/electrospray-mass spectrometry analysis of purified **FMO3** identified >70% of the tryptic peptides, including fragments containing motifs for N-linked glycosylation and O-linked glycosylation. Although insect cells have the capacity for glycan modification, MS analysis of the tryptic peptides demonstrated that these sites were not modified in the purified, recombinant enzyme. Edman degradation of the recombinant product revealed that posttranslational modification of **human FMO3** by insect cells was limited to cleavage at the N-terminal methionine, a process seen in vivo with animal orthologs of **FMO3**. These studies demonstrate the suitability of this eukaryotic system for heterologous expression of **human FMOs** and future detailed analysis of their substrate specificities.

L13 ANSWER 20 OF 42 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:486050 BIOSIS
DOCUMENT NUMBER: PREV199799785253
TITLE: Determination of FAD-binding domain in flavin-containing monooxygenase 1 (FMO1.
AUTHOR(S): Kubo, Akiko; Itoh, Susumu (1); Itoh, Kunio; Kamataki, Tetsuya
CORPORATE SOURCE: (1) Ludwig Inst. Cancer Res., Box 595, S-751 24 Uppsala Sweden
SOURCE: Archives of Biochemistry and Biophysics, (1997) Vol. 345, No. 2, pp. 271-277.

ISSN: 0003-9861.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The flavin-containing monooxygenases (**FMOs**) are a family of flavoenzymes and contain one molecule of FAD per monomer. In order to demonstrate where FMO interacts with FAD, four mutants for the rat **liver** FMO1 protein were expressed in yeast and characterized. All four mutants were immunochemically similar to the unmodified form, although the contents of FAD in all four mutants were much lower than that in the unmodified form. Interestingly, the mutant generated by changing the first glycine of the proposed FAD-binding domain (GxGxxG) to alanine revealed catalytic activities, but was lower than those seen with the unmodified form. The conversion of the first glycine to alanine markedly increased and decreased the K-m and V-max values for imipramine N-oxidation, respectively. The other three mutants (RFMOm2, RFMOm3, and RFMOm4) were catalytically inactive. Our results suggest that three glycines, especially the second and third glycines, in the proposed FAD-binding domain were necessary for FMO to show catalytic activities. Using RFMOm1 and the unmodified form, the effects of n-octylamine on the activity of FMO1 were investigated. The activities of both wild-type and RFMOm1 enzymes for all of the compounds examined were enhanced by n-octylamine. The K-m and V-max values of both RFMOm1 and the unmodified form for imipramine N-oxidation were lowered and raised by n-octylamine, respectively.

L13 ANSWER 21 OF 42 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 1998086483 MEDLINE
DOCUMENT NUMBER: 98086483 PubMed ID: 9417913
TITLE: Structural organization of the **human** flavin-containing monooxygenase 3 gene (**FMO3**), the favored candidate for fish-odor syndrome, determined directly from genomic **DNA**.
AUTHOR: Dolphin C T; Riley J H; Smith R L; Shephard E A; Phillips I R
CORPORATE SOURCE: Department of Biochemistry, Queen Mary & Westfield College, University of London, United Kingdom.
SOURCE: GENOMICS, (1997 Dec 1) 46 (2) 260-7.
Journal code: GEN; 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U39960; GENBANK-U39961; GENBANK-U39962; GENBANK-U39963; GENBANK-U39964; GENBANK-U39965; GENBANK-U39966; GENBANK-U39967
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980203
AB The inherited metabolic disorder trimethylaminuria (fish-odor syndrome) is associated with defective hepatic N-oxidation of dietary-derived trimethylamine catalyzed by flavin-containing monooxygenase (FMO). As **FMO3** encodes the major form of FMO expressed in adult **human liver**, it represents the best candidate gene for the disorder. The structural organization of **FMO3** was determined by sequencing the products of exon-to-exon and vectorette PCR, the latter through the use of vectorette libraries constructed directly from genomic **DNA**. The gene contains one noncoding and eight coding exons. Knowledge of the exon/intron organization of the **human** **FMO3** gene enabled each of the coding exons of the gene, together with their associated flanking intron sequences, to be amplified from genomic **DNA** and will thus facilitate the identification of mutations in **FMO3** in families affected with fish-odor syndrome.

L13 ANSWER 22 OF 42 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97231261 MEDLINE
DOCUMENT NUMBER: 97231261 PubMed ID: 9076656
TITLE: Molecular cloning of mouse **liver** flavin containing monooxygenase (FMO1) **cDNA** and characterization of the expression product: metabolism of the neurotoxin, 1,2,3,4-tetrahydroisoquinoline (TIQ).
AUTHOR: Itoh K; Nakamura K; Kimura T; Itoh S; Kamataki T
CORPORATE SOURCE: Division of Drug Metabolism, Faculty of Pharmaceutical Sciences, Hokkaido University, Japan.
SOURCE: JOURNAL OF TOXICOLOGICAL SCIENCES, (1997 Feb) 22 (1) 45-56.
Journal code: KAE; 7805798. ISSN: 0388-1350.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970609
Last Updated on STN: 19970609
Entered Medline: 19970529

AB A mouse **liver cDNA** clone, MFMO1, coding for a flavin-containing monooxygenase (FMO) was isolated. This **cDNA** clone encoded a protein of 532 amino acids. Based upon its predicted amino acid sequence, this clone was assumed to belong to the FMO1 subfamily. The deduced amino acid sequence showed 94, 84, 83, and 83% identity with FMO1s of rats, pigs, rabbits and humans, respectively, while it showed only 50-59% identity with **human FMO3** and FMO4, rabbit FMO2, **FMO3**, FMO4 and FMO5, and guinea-pig FMO2. **RNA** blot analysis showed that the mouse FMO1 was also expressed in the lung and kidney and to lesser extents in the heart, spleen, testis and brain. Mouse FMO1 expressed in yeast showed activities of thiobenzamide S-oxidation, and NADPH oxidation associated with the S- or N-oxidation of chlorpromazine, N,N-dimethylaniline, N,N-dimethyl-hydrazine, imipramine, nicotine, thioacetamide, thiourea and trimethylamine. Moreover, 1,2,3,4-tetrahydroisoquinoline (TIQ), a substance known to induce a parkinsonism-like syndrome in monkeys, was also metabolized by the mouse FMO1. The K(m) values for chlorpromazine, imipramine and TIQ were determined to be 2,4, 16.0, 435 mM, respectively. This is the first report to show that an expressed FMO can metabolize a neurotoxin, TIQ.

L13 ANSWER 23 OF 42 MEDLINE
ACCESSION NUMBER: 97450419 MEDLINE
DOCUMENT NUMBER: 97450419 PubMed ID: 9305407
TITLE: Quantitation and kinetic properties of hepatic microsomal and recombinant flavin-containing monooxygenases 3 and 5 from humans.
AUTHOR: Overby L H; Carver G C; Philpot R M
CORPORATE SOURCE: Laboratory of Signal Transduction, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA.
SOURCE: CHEMICO-BIOLOGICAL INTERACTIONS, (1997 Aug 29) 106 (1) 29-45.
Journal code: CYV; 0227276. ISSN: 0009-2797.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971024
Last Updated on STN: 19971024
Entered Medline: 19971016

AB Variable amounts of flavin-containing monooxygenase isoforms 3 and 5 (**FMO3** and FMO5) are present in microsomal preparations from adult, male, **human liver**. Quantitation with monospecific antibodies and recombinant isoforms as standards showed levels of **FMO3** and of FMO5 that ranged from 12.5 to 117 and 3.5 to 34 pmol/mg microsomal protein, respectively. The concentration of **FMO3** was greater than that of FMO5 in all samples, but the ratio of **FMO3** to FMO5 varied from 2:1 to 10:1. **Human** hepatic microsomal samples also showed variable activities for the S-oxidation of methimazole. This activity was associated totally with **FMO3**; no participation of FMO5 was apparent. This conclusion was supported by several lines of evidence: first, the catalytic efficiency of **FMO3** with methimazole was found to be approximately 5000 times greater than that of FMO5; second, the rate of metabolism showed a direct, quantitative relationship with **FMO3** content; third, the plot of the relationship between metabolism and **FMO3** content extrapolated close to the origin. A second reaction, the N-oxidation of ranitidine, exhibited a much higher Km with recombinant **FMO3** than did methimazole (2 mM vs. 35 microM). However, a direct relationship between this reaction and **FMO3** content in **human** hepatic microsomal preparations was also apparent. This result shows that even with a high Km substrate, **FMO3**-catalyzed metabolism can account for the majority of the product formation with some drugs. Our findings demonstrate that the contribution of FMO isoforms to **human** hepatic drug metabolism can be assessed quantitatively on the basis of the characteristics of the enzymes expressed in Escherichia coli.

L13 ANSWER 24 OF 42 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 1998008021 MEDLINE
DOCUMENT NUMBER: 98008021 PubMed ID: 9344459
TITLE: Molecular cloning, sequencing, and expression in

Escherichia coli of mouse flavin-containing monooxygenase 3 (**FMO3**): comparison with the **human** isoform.
AUTHOR: Falls J G; Cherrington N J; Clements K M; Philpot R M; Levi P E; Rose R L; Hodgson E
CORPORATE SOURCE: Department of Toxicology, North Carolina State University, Raleigh, North Carolina 27695, USA.
CONTRACT NUMBER: ES00044 (NIEHS)
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1997 Nov 1) 347 (1) 9-18.
Journal code: 6SK; 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U87147
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971202

AB The sequence of mouse flavin-containing monooxygenase 3 (**FMO3**) was obtained from several clones isolated from a mouse **liver** **cDNA** library. The **nucleotide** sequence of mouse **FMO3** was 2020 bases in length containing 37 bases in the 5' flanking region, 1602 in the coding region, and 381 in the 3' flanking region. The derived protein sequence consisted of 534 amino acids including the putative flavin adenine dinucleotide and NADP+ pyrophosphate binding sites (characteristic of mammalian **FMOs**) starting at positions 9 and 191, respectively. The mouse **FMO3** protein sequence was 79 and 82% identical to the **human** and rabbit **FMO3** sequences, respectively. Mouse **FMO3** was expressed in Escherichia coli and compared to E. coli expressed **human** **FMO3**. The **FMO3** proteins migrated with the same mobility (approximately 58 kDa) as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and immunoblotting. The expressed **FMO3** enzymes (mouse and **human** forms) were sensitive to heat and reacted in a similar manner toward metal ions and detergent. Catalytic activities of mouse and **human** **FMO3** were high toward the substrate methimazole; however, in the presence of trimethylamine and thioacetamide, FMO-dependent methimazole oxidation by both enzymes was reduced by greater than 85%. Other substrates which inhibited methimazole oxidation were thiourea and thiobenzamide and to a lesser degree N,N-dimethylaniline. When probed with mouse **FMO3** **cDNA**, **FMO3** transcripts were detected in hepatic **mRNA** samples from female mice, but not in samples from males. **FMO3** was detected in **mRNA** samples from male and female mouse lung, but **FMO3** message was not detected in mouse kidney sample from either gender. Results of immunoblotting confirmed the tissue- and gender-dependent expression of mouse **FMO3**.

L13 ANSWER 25 OF 42 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 97057945 MEDLINE
DOCUMENT NUMBER: 97057945 PubMed ID: 8902275
TITLE: N-oxygenation of primary amines and hydroxylamines and retroreduction of hydroxylamines by adult **human** **liver** microsomes and adult **human** flavin-containing monooxygenase 3.
AUTHOR: Lin J; Berkman C E; Cashman J R
CORPORATE SOURCE: Seattle Biomedical Research Institute, Washington 98108, USA.
CONTRACT NUMBER: GM36426 (NIGMS)
SOURCE: CHEMICAL RESEARCH IN TOXICOLOGY, (1996 Oct-Nov) 9 (7) 1183-93.
Journal code: A5X; 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19970305
Entered Medline: 19970220

AB Adult **human** **liver** microsomes catalyze the NADPH-dependent N-oxygenation of 10-N-(n-octylamino)-2-(trifluoromethyl)phenothiazine to the corresponding oximes through the intermediacy of the hydroxylamine. In the presence of adult **human** **liver** microsomes, the primary amine is stereoselectively converted

to the cis-oxime, but addition of the alternative competitive substrate hydroxylamine hydrochloride apparently decreases the amount of aliphatic hydroxylamine retroreduction because an increase in oxime formation was observed. In the presence of hydroxylamine hydrochloride, however, the oxime product recovered was formed with very low stereoselectivity. Studies on the biochemical mechanism of oxime formation suggested that cis-oxime formation in the presence of adult **human liver** microsomes was largely dependent on the **human** flavin-containing monooxygenase (form 3). This conclusion is based on the effects of incubation conditions on product formation when compared to results observed in the presence of **cDNA**-expressed **human** **FMO3**. The retroreduction of the intermediate hydroxylamine was dependent on NADPH but was not catalyzed by **human** flavin-containing monooxygenase (form 3) or any one of seven prominent cytochromes P-450 that have been well-characterized in the **human** **liver** microsomes examined. The results suggest that aliphatic primary amines are efficiently sequentially N-oxygenated in the presence of **human liver** microsomes to hydroxylamines and then to oximes mainly by the **human** flavin-containing monooxygenase. Retroreduction of the intermediate hydroxylamine is apparently facilitated by a novel but as yet poorly characterized enzyme system that does not employ any of the currently known well-characterized cytochrome P-450 enzymes present in adult **human liver** microsomes.

L13 ANSWER 26 OF 42 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 96184548 MEDLINE
DOCUMENT NUMBER: 96184548 PubMed ID: 8654418
TITLE: Differential developmental and tissue-specific regulation of expression of the genes encoding three members of the flavin-containing monooxygenase family of man, FMO1, **FMO3** and FM04.
AUTHOR: Dolphin C T; Cullingford T E; Shephard E A; Smith R L; Phillips I R
CORPORATE SOURCE: Department of Biochemistry, Queen Mary & Westfield College, University of London, UK.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1996 Feb 1) 235 (3) 683-9.
Journal code: EMZ; 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Z47552
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960808
Last Updated on STN: 19960808
Entered Medline: 19960730

AB We have previously described the isolation and sequencing of **cDNA** clones encoding flavin-containing monooxygenases (**FMOs**) 1 and 4 of man [Dolphin, C., Shephard, E. A., Povey, S., Palmer, C. N. A., Ziegler, D. M., Ayesh, R., Smith, R. L. & Phillips, I. R. (1991) J. Biol. Chem. 266, 12379-12385; Dolphin, C., Shephard E. A., Povey, S., Smith, R. L. & Phillips, I. R. (1992) Biochem. J. 287, 261-267]. We present here the isolation of a **cDNA** for FM03 of man. The sequence of this **CDNA** and the amino acid sequence deduced from it differ substantially from those previously reported for this member of the FMO family of man. In addition, we have investigated, by quantitative RNase protection assays, the expression in several foetal and adult **human** tissues of genes encoding FMO1, **FMO3** and FM04, Our results demonstrate that, in the adult, FMO1 is expressed in kidney but not in **liver**, whereas in the foetus it is expressed in both organs. The lack of expression of FMO1 in adult **human** **liver** is in marked contrast to the situation in other mammals, such as pig and rabbit, in which FMO1 constitutes a major form of the enzyme in the **liver** of the adult animal. The **mRNA** encoding **FMO3** is abundant in adult **liver** and is also present, in low abundance, in some foetal tissues. Thus, FMO1 and **FMO3** are both subject to developmental and tissue-specific regulation, with a developmental switch in the expression of the genes taking place in the **liver**. FMO4 **mRNA** is present in low abundance in several foetal and adult tissues and thus the corresponding gene appears to be expressed constitutively.

L13 ANSWER 27 OF 42 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 96223482 MEDLINE
DOCUMENT NUMBER: 96223482 PubMed ID: 8632334
TITLE: Identification of the **human** cytochromes P450 responsible for the in vitro formation of the major

oxidative metabolites of the antipsychotic agent olanzapine.
AUTHOR: Ring B J; Catlow J; Lindsay T J; Gillespie T; Roskos L K; Cerimele B J; Swanson S P; Hamman M A; Wrighton S A
CORPORATE SOURCE: Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA.
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1996 Feb) 276 (2) 658-66.
Journal code: JP3; 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 19960715
Entered Medline: 19960703

AB The formation kinetics of 2-hydroxymethyl olanzapine (2-OH olanzapine), 4'-N-oxide olanzapine (N-O olanzapine) and 4'-N-desmethyl olanzapine (NdM olanzapine) were analyzed in vitro. Biphasic kinetics were observed for formation of 2-OH and NdM olanzapine. The high-affinity enzyme responsible for 2-OH olanzapine formation by two **human liver** samples exhibited an intrinsic clearance (CLint) of 0.2 microliter/min/mg. NdM olanzapine formation by two **human liver** samples exhibited a CLint of 1.0 microliter/min/mg for the high affinity enzyme. The formation of N-O olanzapine was linear up to 300 microM olanzapine, yielding a CLint of 0.32 to 1.70 microliters/min/mg. The formation of 7-hydroxy olanzapine (7-OH olanzapine) exhibited an apparent Km of 24.2 microM. The rates of 2-OH olanzapine formation correlated with CYP2D6 levels and activity, and it was formed to the greatest extent by **cDNA**-expressed CYP2D6. N-O olanzapine formation correlated with **human liver** flavin-containing monooxygenase (**FMO3**) levels and activity. NdM olanzapine and 7-OH olanzapine formation correlated with CYP1A2 catalytic activities and they were formed to the greatest extent by expressed CYP1A2. These results suggest that CYP1A2 catalyzes NdM olanzapine and 7-OH olanzapine formation, CYP2D6 catalyzes 2-OH olanzapine formation and **FMO3** catalyzes N-O olanzapine formation.

L13 ANSWER 28 OF 42 MEDLINE
ACCESSION NUMBER: 96374838 MEDLINE
DOCUMENT NUMBER: 96374838 PubMed ID: 8786146
TITLE: Localization of **human** flavin-containing monooxygenase genes FMO2 and FMO5 to chromosome 1q.
AUTHOR: McCombie R R; Dolphin C T; Povey S; Phillips I R; Shephard E A
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University College London, Gower Street, London, WC1E 6BT, United Kingdom.
SOURCE: GENOMICS, (1996 Jun 15) 34 (3) 426-9.
Journal code: GEN; 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961008
Last Updated on STN: 19961008
Entered Medline: 19960924

AB The **human** flavin-containing monooxygenase (FMO) gene family comprises at least five distinct members (FMO1 to FMO5) that code for enzymes responsible for the oxidation of a wide variety of soft nucleophilic substrates, including drugs and environmental pollutants. Three of these genes (FMO1, **FMO3**, and FMO4) have previously been localized to **human** chromosome 1q, raising the possibility that the entire gene family is clustered in this chromosomal region. Analysis by polymerase chain reaction of **DNA** isolated from a panel of **human**-rodent somatic cell hybrids demonstrates that the two remaining identified members of the FMO gene family, FMO2 and FMO5, also are located on chromosome 1q.

L13 ANSWER 29 OF 42 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 96115258 MEDLINE
DOCUMENT NUMBER: 96115258 PubMed ID: 8654204
TITLE: In vitro hepatic metabolism of ABT-418 in chimpanzee (Pan troglodytes). A unique pattern of microsomal flavin-containing monooxygenase-dependent stereoselective

N'-oxidation.
AUTHOR: Rodrigues A D; Kukulka M J; Ferrero J L; Cashman J R
CORPORATE SOURCE: Drug Metabolism Department, Abbott Laboratories, Abbott Park, IL 60064-3500, USA.
CONTRACT NUMBER: GM36426 (NIGMS)
SOURCE: DRUG METABOLISM AND DISPOSITION, (1995 Oct) 23 (10) 1143-52.
Journal code: EBR; 9421550. ISSN: 0090-9556.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960808
Last Updated on STN: 19980206
Entered Medline: 19960726

AB Metabolism of the cholinergic channel activator [N-methyl-3H]ABT-418 was studied using precision-cut tissue slices and microsomes (+/- cytosol) prepared from a single chimpanzee **liver**. In both cases, the products of C-oxidation (lactam) and N'-oxidation (cis > trans) were detected. In the presence of chimpanzee **liver** microsomes and cytosol, which had been characterized with respect to the levels of aldehyde oxidase (N1-methylnicotinamide oxidase), NADPH-dependent flavin-containing monooxygenase (FMO; N, N-dimethylaniline N-oxidase), and various cytochrome P450 (CYP)-dependent monooxygenase activities, ABT-418 lactam and N'-oxide formation was found to be largely dependent on CYP/aldehyde oxidase and FMO, respectively. The rank order of total (trans + cis) FMO-dependent N'-oxidation in **liver** microsomes was dog > rat > rabbit > chimpanzee > or = cynomolgus monkey > **human**. It is concluded that the metabolic profile of ABT-418 in the chimpanzee is unique. First, the C-/N'-oxidation ratio in **liver** slices (0.43) is similar to that of the rat and dog and dissimilar to that of the rat and dog and dissimilar to that of the two other primate species studied; **human** and cynomolgus monkey (C-/N'-oxidation ratio > or = 9.4). Second, the pattern of ABT-418 N'-oxidation observed with chimpanzee **liver** microsomes, and **liver** slices (trans:cis = 1:3), differs from that of rat, rabbit, and dog **liver** microsomes, rat and **human** kidney S-9 (trans >> cis), **human** **liver** microsomes (trans:cis approximately 1:1), and cynomolgus monkey (trans:cis approximately 2:1) **liver** microsomes. Lack of stereoselective N'-oxidation by **human** FMO was confirmed with **cDNA**-expressed **FMO3**.

L13 ANSWER 30 OF 42 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 95374576 MEDLINE
DOCUMENT NUMBER: 95374576 PubMed ID: 7646564
TITLE: In vitro-in vivo correlations of **human** (S)-nicotine metabolism.
AUTHOR: Berkman C E; Park S B; Wrighton S A; Cashman J R
CORPORATE SOURCE: Seattle Biomedical Research Institute, WA 98109, USA.
CONTRACT NUMBER: TT016614
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1995 Aug 8) 50 (4) 565-70.
Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950930
Last Updated on STN: 19950930
Entered Medline: 19950920

AB The profile of (S)-nicotine metabolism in **human** **liver** microsomes was examined at concentrations approaching in vivo conditions (10 microM). At such concentrations, no (S)-nicotine N-1'-oxygenation was seen, and thus C-oxidation to the (S)-nicotine delta 1',5'-iminium ion was the sole product observed in the metabolic profile in the presence of the **human** **liver** microsomes. For simplicity of analysis, the (S)-nicotine delta 1',5'-iminium ion formed was converted to (S)-cotinine in the presence of exogenously added aldehyde oxidase. To explain the lack of (S)-nicotine N-1'-oxygenation at low (S)-nicotine concentrations, inhibition of flavin-containing monooxygenase (FMO) activity by (S)-cotinine was examined. Although (S)-cotinine was observed to inhibit pig FMO1 (Ki = 675 microM), partially purified **cDNA**-expressed adult **human** **liver** **FMO3** was not inhibited by (S)-cotinine. We therefore concluded that the kinetic properties of the nicotine N'- and C-oxidases were responsible for the metabolic product profile observed. Kinetic constants were determined for individual **human** **liver** microsomal preparations from low (10 microM)

and high (500 microM) (S)-nicotine concentrations by monitoring (S)-cotinine formation with HPLC. The mean Kmapp and Vmax for formation of (S)-cotinine by the microsomes examined were 39.6 microM and 444.3 pmol.min-1.(mg protein)-1, respectively. The formation of (S)-cotinine was strongly dependent on the previous drug administration history of each subject, and among the highest rates for (S)-cotinine formation were those of the barbiturate-pretreated subjects. The rate of (S)-cotinine formation at low (10 microM) concentration correlated well with immunoreactivity for cytochrome P450 2A6 (r = 0.89). In vitro-in vivo correlation of the results suggests that the low amount of (S)-nicotine N-1'-oxygenation and the large amount of (S)-cotinine formed in **human** smokers (i.e. 4 and 30% of a typical dose, respectively) are determined primarily by the kinetic properties of the **human** monooxygenase enzyme systems. However, additional non-hepatic monooxygenase(s) contributes to (S)-nicotine metabolism.

L13 ANSWER 31 OF 42 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 95177663 MEDLINE
DOCUMENT NUMBER: 95177663 PubMed ID: 7872795
TITLE: Characterization of flavin-containing monooxygenase 5 (FMO5) cloned from **human** and guinea pig: evidence that the unique catalytic properties of FMO5 are not confined to the rabbit ortholog.
AUTHOR: Overby L H; Buckpitt A R; Lawton M P; Atta-Asafo-Adjei E; Schulze J; Philpot R M
CORPORATE SOURCE: Molecular Pharmacology Section, National Institutes of Environmental Health Sciences, Research Triangle Park, North Carolina 27709.
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1995 Feb 20) 317 (1) 275-84.
Journal code: 6SK; 0372430. ISSN: 0003-9861.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L37080; GENBANK-L37081
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950407
Last Updated on STN: 19950407
Entered Medline: 19950329

AB Several full-length clones encoding the **human** and guinea pig orthologs of flavin-containing monooxygenase 5 (FMO5) have been isolated from libraries constructed with hepatic **mRNA**. The clones were detected by hybridization with the **cDNA** encoding FMO5 expressed in rabbit. The **human** and guinea pig cDNAs encode for proteins of 533 amino acids that contain putative pyrophosphate binding domains characteristic of mammalian **FMOs**. The sequences derived for the **human** and guinea pig FMO5 proteins are 87% identical and are 85 and 82% identical, respectively, to the sequence of rabbit FMO5. As is the case with other **FMOs**, FMO5 in **human** and guinea pig is encoded by multiple transcripts. Rabbit FMO5 expressed in Escherichia coli was purified and used to elicit antibodies in goat. These antibodies detected FMO5 in samples from livers of adult humans, rabbits, and guinea pigs and fetal livers of humans. The **human** and guinea pig forms of FMO5 were expressed in E. coli and characterized. Neither enzyme effectively catalyzed the metabolism of methimazole, a general FMO substrate; however, both were active with n-octylamine. The responses of the **human** FMO5 and guinea pig FMO5 to detergent, ions and elevated temperature are all similar to the responses described for rabbit FMO5. These results indicate that the unique properties of FMO5 from rabbit are species-independent and that this form of the flavin-containing monooxygenase is not readily classified as a drug-metabolizing enzyme.

L13 ANSWER 32 OF 42 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 95236487 MEDLINE
DOCUMENT NUMBER: 95236487 PubMed ID: 7720103
TITLE: Role of hepatic flavin-containing monooxygenase 3 in drug and chemical metabolism in adult humans.
AUTHOR: Cashman J R; Park S B; Berkman C E; Cashman L E
CORPORATE SOURCE: Seattle Biomedical Research Institute, WA 98109, USA.
CONTRACT NUMBER: GM36426 (NIGMS)
SOURCE: CHEMICO-BIOLOGICAL INTERACTIONS, (1995 Apr 28) 96 (1) 33-46. Ref: 55
Journal code: CYV; 0227276. ISSN: 0009-2797.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950605
Last Updated on STN: 19950605
Entered Medline: 19950525

AB In conjunction with asymmetric chemical syntheses and spectral, chiroptical, chromatographic and stereochemical correlation methods, we have developed procedures for the quantification of sulfoxide enantiomers and tertiary amine N-oxide diastereomer metabolites arising from the action of the adult **human liver** and other flavin-containing monooxygenases (**FMOs**). The parallel nature of the metabolic in vitro-in vivo studies and the use of chemical model oxidation systems allowed us to identify the FMO isoform involved. We investigated the enantioselective S-monooxygenation of cimetidine and the diastereoselective tertiary amine N-1'-oxygenation of (S)-nicotine as stereoselective functional probes of adult **human liver** FMO action. In both cases, the majority of evidence points to adult **human liver FMO3** as the principal enzyme responsible for cimetidine S-oxygenation and (S)-nicotine N-1'-oxygenation in vitro and in vivo. The excellent agreement between the absolute configuration of the major cimetidine S-oxide and (S)-nicotine N-1'-oxide metabolites isolated from **human** urine and the major metabolite formed in the presence of adult **human liver** microsomes suggests that in vitro hepatic preparations may serve as a useful model for the in vivo condition. Further, that adult **human liver cDNA**-expressed **FMO3** in Escherichia coli also gave the same absolute stereoselectivity (i.e. for (S)-nicotine N-1'-oxygenation) confirms the identity of the monoxygenase in vivo. Although we cannot rule out the involvement of minor contributions of cytochrome P-450 monooxygenases in cimetidine and (S)-nicotine oxidation, the majority of the data support the fact that cimetidine S-oxygenation and (S)-nicotine N-1'-oxygenation are stereoselective functional probes of adult **human liver FMO3** activity. Finally, because the stereochemistry of the principal metabolite of cimetidine and (S)-nicotine in small experimental animals is distinct from that observed in humans, it is likely that species variation in predominant FMO isoforms exist and this may have important consequences for the choice of experimental animals in **human** preclinical drug design and development programs.

L13 ANSWER 33 OF 42 MEDLINE DUPLICATE 24
ACCESSION NUMBER: 95236485 MEDLINE
DOCUMENT NUMBER: 95236485 PubMed ID: 7720101
TITLE: The molecular biology of the flavin-containing monooxygenases of man.
AUTHOR: Phillips I R; Dolphin C T; Clair P; Hadley M R; Hutt A J; McCombie R R; Smith R L; Shephard E A
CORPORATE SOURCE: Department of Biochemistry, Queen Mary and Westfield College, University of London, UK.
SOURCE: CHEMICO-BIOLOGICAL INTERACTIONS, (1995 Apr 28) 96 (1) 17-32.
Journal code: CYV; 0227276. ISSN: 0009-2797.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950605
Last Updated on STN: 19950605
Entered Medline: 19950525

AB **cDNA** clones encoding five distinct members of the FMO family of man (**FMOs** 1, 2, 3, 4 and 5) were isolated by a combination of library screening and reverse transcription-polymerase chain reaction techniques. The deduced amino acid sequences of the **human FMOs** have 82-87% identity with their known orthologues in other mammal but only 51-57% similarity to each other. The hydropathy profiles of the proteins are very similar. From the calculated rate of evolution of **FMOs** (a 1% change in sequence per 6 million years) it would appear that individual members of the FMO gene family arose by duplication of a common ancestral gene some 250-300 million years ago. Each of the FMO genes was mapped by the polymerase chain reaction to the long arm of **human** chromosome 1. The localization of the FMO1 gene was further refined to 1q23-q25 by in situ hybridization of **human** metaphase chromosomes. RNase protection assays demonstrated that in man each FMO gene displays a distinct developmental and tissue-specific pattern of expression. In the adult, FMO1 is expressed in kidney but not in **liver**, whereas in the foetus its **mRNA** is abundant in

both organs. **FMO3** expression is essentially restricted to the **liver** in the adult and the **mRNA** is either absent, or present in low amounts, in foetal tissues. FMO4 is expressed more constitutively. **Human** FMO1 and **FMO3** cDNAs were functionally expressed in prokaryotic and eukaryotic cells. FMO1 and **FMO3**, expressed in either system, displayed product stereoselectivity in their catalysis of the N-oxidation of the pro-chiral tertiary amines, N-ethyl-N-methylaniline (EMA) and pargyline. Both enzymes were stereoselective with respect to the production of the (-)-S-enantiomer of EMA N-oxide. But in the case of pargyline, the enzymes displayed opposite stereoselectivity, FMO1 producing solely the (+)-enantiomer and **FMO3** predominantly the (-)-enantiomer of the N-oxide.

L13 ANSWER 34 OF 42 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 95236486 MEDLINE
DOCUMENT NUMBER: 95236486 PubMed ID: 7720102
TITLE: Prochiral sulfides as in vitro probes for multiple forms of the flavin-containing monooxygenase.
AUTHOR: Rettie A E; Meier G P; Sadeque A J
CORPORATE SOURCE: Department of Medicinal Chemistry, University of Washington, Seattle 98195, USA.
SOURCE: CHEMICO-BIOLOGICAL INTERACTIONS, (1995 Apr 28) 96 (1) 3-15. Journal code: CYV; 0227276. ISSN: 0009-2797.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950605
Last Updated on STN: 19950605
Entered Medline: 19950525

AB A homologous series of alkyl-substituted p-tolyl sulfides have been synthesized and evaluated as in vitro, isozyme-selective substrate probes for the microsomal flavin containing monooxygenases. Straight-chain and branched-chain alkyl homologs were metabolized to the corresponding (R)- and (S)-sulfoxides which were analyzed by chiral phase high-performance liquid chromatography. Initial studies demonstrated that the stereochemical composition of alkyl p-tolyl sulfoxides generated by FMO2, purified from rabbit lung, was a function of the degree of steric crowding about the prochiral center. In contrast, purified rabbit **liver** FMO1 formed the (R)-sulfoxide from the n-alkyl series of substrates in a highly stereoselective manner (> 90%). Similar results were obtained with these two rabbit cDNAs expressed in E. coli. In contrast to rabbit FMO1 and FMO2, a characteristic feature of catalysis by **cDNA** -expressed rabbit **FMO3** was the lack of stereoselectivity observed for formation of methyl p-tolyl sulfoxide. Collectively, these data demonstrate that the stereochemical composition of sulfoxides generated from the n-alkyl series of sulfides is isozyme-dependent. Metabolism of methyl p-tolyl sulfide by detergent-solubilized hepatic microsomes from a wide variety of experimental animals yielded predominantly (R)- methyl p-tolyl sulfoxide, which, at least in rabbit **liver**, is indicative of catalysis dominated by FMO1. However, solubilized **human** and macaque **liver** preparations catalyzed this reaction in a relatively non-stereoselective manner. Macaque **liver** FMO was purified and the metabolite profile generated from the n-alkyl p-tolyl sulfides was found to be most similar to rabbit **FMO3**. Moreover, antibodies directed against macaque **liver** FMO selectively reacted with rabbit **FMO3** and a microsomal protein expressed in adult **human**, but not fetal **human liver**, adult **human** kidney or adult **human** lung. Therefore, an FMO isoform expressed selectively in adult primate **liver** has catalytic and immunochemical properties consistent with its classification in the **FMO3** family.

L13 ANSWER 35 OF 42 MEDLINE DUPLICATE 26
ACCESSION NUMBER: 94145088 MEDLINE
DOCUMENT NUMBER: 94145088 PubMed ID: 8311461
TITLE: A nomenclature for the mammalian flavin-containing monooxygenase gene family based on amino acid sequence identities.
AUTHOR: Lawton M P; Cashman J R; Cresteil T; Dolphin C T; Elfarra A A; Hines R N; Hodgson E; Kimura T; Ozols J; Phillips I R; +
CORPORATE SOURCE: National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709.
SOURCE: ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1994 Jan) 308 (1) 254-7.
Journal code: 6SK; 0372430. ISSN: 0003-9861.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
ENTRY DATE: Entered STN: 19940330
Last Updated on STN: 19990129
Entered Medline: 19940315

AB A nomenclature based on comparisons of amino acid sequences is proposed for the members of the mammalian flavin-containing monooxygenase (FMO) gene family. This nomenclature is based on evidence of a single gene family composed of five genes. The percentage identities of the amino acid sequences of the five known forms of mammalian FMO are between 52 and 57% in rabbit and between 50 and 58% across species lines. The identities of all orthologs are greater than 82%. There is no evidence for multiple, highly related forms of the enzyme or for more than one mammalian FMO gene family. In the proposed system, the mammalian flavin-containing monooxygenase gene family is designated as "FMO" and the individual genes are distinguished by an Arabic numeral. The **FMOs** known as the "**liver**" and "lung" enzymes become FMO1 and FMO2, and the more recently described forms of the enzymes become **FMO3**, FMO4, and FMO5. **Human** FMO gene designations, FMO1 and **FMO3**, remain unchanged, but the gene designated FMO2 becomes FMO4. Following convention, the genes and **cDNA** designations will be italicized and the **mRNA** and protein designations will be nonitalicized. The purpose of the proposed nomenclature is to provide for the unambiguous identification of orthologous forms of mammalian **FMOs**, regardless of the species or tissue in question. The proposed classification considers only members of the mammalian flavin-containing monooxygenase gene family and has no bearing on the generally accepted definition of a multisubstrate flavin-containing monooxygenase.

L13 ANSWER 36 OF 42 MEDLINE DUPLICATE 27
ACCESSION NUMBER: 93252844 MEDLINE
DOCUMENT NUMBER: 93252844 PubMed ID: 8486656
TITLE: Cloning, sequencing, distribution, and expression in Escherichia coli of flavin-containing monooxygenase 1C1. Evidence for a third gene subfamily in rabbits.
AUTHOR: Atta-Asafo-Adjei E; Lawton M P; Philpot R M
CORPORATE SOURCE: Laboratory of Cellular and Molecular Pharmacology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1993 May 5) 268 (13) 9681-9.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L08449
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19970203
Entered Medline: 19930604

AB Two full-length **cDNA** clones (2.2 kilobases) encoding a newly recognized form of mammalian flavin-containing monooxygenase (FMO) have been isolated from independent libraries constructed with **mRNA** from different rabbits. The cDNAs encode a polypeptide of 533 amino acids which contains two putative pyrophosphate binding domains and a hydrophobic carboxyl terminus characteristic of **FMOs**. This sequence is 52 and 57% identical to sequences of the rabbit "hepatic" and "pulmonary" **FMOs**, respectively, and 55% identical to the sequence of "**liver** form 2" published recently by Ozols (Ozols, J. (1991) Arch. Biochem. Biophys. 290, 103-115). **cDNA** for the new FMO (FMO 1C1) hybridizes with two species of **mRNA**, one of 2.6 kilobases and one of about 5.4 kilobases, from **liver** or kidney, but not lung. Guinea pig, hamster, rat, and mouse all express this form of FMO in **liver**, kidney, and lung. FMO 1C1 has been tentatively characterized following expression in Escherichia coli. It is inactive with methimazole as substrate but highly active with n-octylamine. The temperature lability, responses to ions and detergent, and pH optimum of FMO 1C1 are similar to values reported for hepatic FMO. Sequence comparisons and analysis of rabbit and **human** genomic **DNA** indicate that FMO 1C1, as well as the pulmonary and hepatic **FMOs**, comprise a single gene family made up of distinct gene subfamilies (A, B,C,D, ... N), each appearing to contain a single gene. A nomenclature, based on these interrelationships and following the same designations used for classifying cytochromes P-450, is proposed.

L13 ANSWER 37 OF 42 MEDLINE DUPLICATE 28
ACCESSION NUMBER: 94162508 MEDLINE
DOCUMENT NUMBER: 94162508 PubMed ID: 8117928
TITLE: Stereoselective metabolism of (S)-(-)-nicotine in humans: formation of trans-(S)-(-)-nicotine N-1'-oxide.
AUTHOR: Park S B; Jacob P 3rd; Benowitz N L; Cashman J R
CORPORATE SOURCE: Department of Pharmaceutical Chemistry and Liver Center, School of Pharmacy, University of California, San Francisco 94143-0446.
CONTRACT NUMBER: NIDA DA01696 (NIDA)
NIDA DA02277 (NIDA)
NIDA GM36426 (NIGMS)
SOURCE: CHEMICAL RESEARCH IN TOXICOLOGY, (1993 Nov-Dec) 6 (6) 880-8.
Journal code: A5X; 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940412
Last Updated on STN: 19970203
Entered Medline: 19940404

AB The chemical synthesis and chromatographic separation of cis- and trans-(S)-nicotine N-1'-oxide diastereomers have allowed the development of methods for the quantification of (S)-nicotine N-1'-oxides during in vitro and in vivo metabolic studies. The metabolism of (S)-nicotine was investigated in the presence of microsomes, **cDNA**-expressed and highly purified flavin-containing monooxygenase (FMO) from pig **liver**, **human liver**, and rabbit lung. For comparison, the N-1'-oxidation of (S)-nicotine in the presence of the cytochrome P450 2B1 from rat **liver**, cytochrome P450 2B10 from mouse **liver**, and cytochrome P450 4A2 from rabbit lung was examined. The ratio of trans:cis (S)-nicotine N-1'-oxide formation for pig **liver** FMO1 (form 1) was 57:43. In contrast, **cDNA** -expressed adult **human liver** **FMO3** (form 3) and rabbit lung FMO2 formed solely trans-(S)-nicotine N-1'-oxide. Of the cytochrome P450 enzymes examined, formation of (S)-nicotine N-1'-oxide occurred with a mean trans:cis ratio of 82:18. The stereoselectivity of (S)-nicotine N-1'-oxide formation was investigated by examining the urine of 13 healthy male smokers studied on a protocol which included free-smoking, intravenous infusion of (S)-nicotine-d2 and dermal patch administration of (S)-nicotine-d0. During cigarette smoking or administration of intravenous or transdermal (S)-nicotine, only the trans diastereomer of (S)-nicotine N-1'-oxide was observed in the urine. That the trans-(S)-nicotine N-1'-oxide metabolite was not appreciably reduced or oxidized further was investigated with infusion studies of (S)-nicotine-d2N-1'-oxide.(ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 38 OF 42 MEDLINE DUPLICATE 29
ACCESSION NUMBER: 94162497 MEDLINE
DOCUMENT NUMBER: 94162497 PubMed ID: 8117918
TITLE: Regio- and stereoselective oxygenations by adult **human liver** flavin-containing monooxygenase 3. Comparison with forms 1 and 2.
AUTHOR: Lomri N; Yang Z; Cashman J R
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco 94143-0446.
CONTRACT NUMBER: GM 36426 (NIGMS)
SOURCE: CHEMICAL RESEARCH IN TOXICOLOGY, (1993 Nov-Dec) 6 (6) 800-7.
Journal code: A5X; 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940412
Last Updated on STN: 19970203
Entered Medline: 19940404

AB The **cDNA** for the adult **human liver** flavin-containing monooxygenase (form 3) (**FMO3**) was cloned, sequenced, and expressed in Escherichia coli. The **cDNA**-expressed **FMO3** was used to investigate the regio- and stereoselective N- and S-oxygenation of a number of tertiary amines and sulfides, respectively. For comparison, the N- and S-oxygenation of the same chemicals and drugs were examined with adult **human liver** microsomes from a

normal healthy female donor and FMO1 from pig **liver** and FMO2 from rabbit lung. Both **cDNA**-expressed **FMO3** and adult **human liver** microsomes N-oxygenated trifluoperazine or 10-(N,N-dimethylaminoalkyl)-phenothiazines with similar substrate specificities. The substrate specificity for **FMO3** differed, however, from that of pig **liver** FMO1. Nucleophilic sulfur-containing compounds [i.e., thiobenzamide, (4-bromophenyl)-1,3-oxathiolane, and 2-methyl-1,3-benzodithiole] were efficiently S-oxygenated by **cDNA**-expressed **FMO3** and adult **human liver** microsomes. Stereoselective S-oxygenation of (+)- and (-)-(4-bromophenyl)-1,3-oxathiolane and 2-methyl-1,3-benzodithiole was therefore investigated. In general, the stereoselectivity observed for S-oxygenation in the presence of **FMO3** was similar to that observed in the presence of adult **human liver** microsomes. In most cases examined, however, the stereoselectivity for S-oxygenation was quite distinct from that observed for pig **liver** FMO1. We conclude that **FMO3** is the major form of FMO active in adult **human liver**. Because the stereoselectivity for X-oxygenation and the substrate specificity for tertiary amine N-oxygenation by **cDNA**-expressed **FMO3** are distinct from those of pig **liver** FMO1, we conclude that the binding channel for each isoform is quite different.(ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 39 OF 42 MEDLINE DUPLICATE 30
ACCESSION NUMBER: 93385451 MEDLINE
DOCUMENT NUMBER: 93385451 PubMed ID: 8374037
TITLE: Expression in Escherichia coli of the flavin-containing monooxygenase D (form II) from adult **human liver**: determination of a distinct tertiary amine substrate specificity.
AUTHOR: Lomri N; Yang Z; Cashman J R
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco 94143-0446.
CONTRACT NUMBER: TT 016614
SOURCE: CHEMICAL RESEARCH IN TOXICOLOGY, (1993 Jul-Aug) 6 (4) 425-9.
Journal code: A5X; 8807448. ISSN: 0893-228X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931105
Last Updated on STN: 19970203
Entered Medline: 19931018

AB The **cDNA** for a major component of the family of flavin-containing monooxygenases (**FMOs**) present in adult **human liver** (i.e., HLFMO-D) has been cloned and expressed in a prokaryotic system. Escherichia coli strain NM522 was transformed with pTrcHLFMO-D, and the HLFMO-D **cDNA** was expressed under the control of the Trc promoter. A variety of tertiary amine substrates [i.e., chlorpromazine and 10-[(N,N-dimethylamino)alkyl]-2-(trifluoromethyl)phenothiazines] were efficiently oxygenated by HLFMO-D **cDNA** expressed in E. coli or by adult **human liver** microsomes. Approximate dimensions of the substrate binding channel for both adult **human liver** microsomal FMO and **cDNA**-expressed HLFMO-D were apparent from an examination of the N-oxygenation of a series of 10-[(N,N-dimethylamino)alkyl]-2-(trifluoromethyl)phenothiazines. The substrate regioselectivity studies suggest that adult **human liver** FMO form D possesses a distinct substrate specificity compared with form A FMO from animal hepatic sources. It is likely that the substrate specificity observed for **cDNA**-expressed adult **human liver** FMO-D may have consequences for the metabolism and distribution of tertiary amines and phosphorus- and sulfur-containing drugs in humans and may provide insight into the physiologic substrate(s) for adult **human liver** FMO.

L13 ANSWER 40 OF 42 MEDLINE DUPLICATE 31
ACCESSION NUMBER: 93277949 MEDLINE
DOCUMENT NUMBER: 93277949 PubMed ID: 8504165
TITLE: Rat **liver** flavin-containing monooxygenase (FMO): **cDNA** cloning and expression in yeast.
AUTHOR: Itoh K; Kimura T; Yokoi T; Itoh S; Kamataki T
CORPORATE SOURCE: Division of Drug Metabolism, Faculty of Pharmaceutical Sciences, Hokkaido University, Japan.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1993 May 28) 1173 (2) 165-71.

Journal code: A0W; 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-D13124; GENBANK-D13127; GENBANK-D13132; GENBANK-D13133; GENBANK-D13134; GENBANK-D13135; GENBANK-D13136; GENBANK-D13137; GENBANK-L08068; GENBANK-M84719
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930716
Last Updated on STN: 19950206
Entered Medline: 19930702

AB A rat **liver cDNA** clone, RFM01, coding for a flavin-containing monooxygenase (FMO) was isolated. This **cDNA** clone encoded a protein of 532 amino acids. The deduced amino acid sequence was 84, 82 and 82% identical to those of the pig, **human** (Form 1) and rabbit (Form 1) **liver FMOs**, while it was only 52, 50, 54, 56 and 54% identical to the **human** (Form II), **human** (Form 2) and rabbit **liver FMOs** (Form 2) and rabbit and guinea pig lung **FMOs**. **RNA** blot analysis showed that rat **liver** FMO was also expressed in lung and kidney and to a lesser extent in the heart and brain. An expression plasmid, pAMFMO, was constructed and the FMO protein expressed in yeast (AH22). This FMO protein catalyzed thiobenzamide S-oxidation, and NADPH oxidation associated with the S- or N-oxidation of thiourea, N,N-dimethylaniline, trimethylamine, imipramine, chlorpromazine, N,N-dimethylhydrazine, thioacetamide as substrates. The S-oxidation activities of thiobenzamide and thiourea were enhanced by n-octylamine, a known enhancer of FMO, and inhibited by alpha-naphthylthiourea, a known inhibitor of FMO. This is the first report in which FMO with catalytic activities was stably expressed.

L13 ANSWER 41 OF 42 MEDLINE DUPLICATE 32
ACCESSION NUMBER: 92179247 MEDLINE
DOCUMENT NUMBER: 92179247 PubMed ID: 1542660
TITLE: Molecular cloning of the flavin-containing monooxygenase (form II) **cDNA** from adult **human liver**.
COMMENT: Erratum in: Proc Natl Acad Sci U S A 1995 Oct 10;92(21):9910
AUTHOR: Lomri N; Gu Q; Cashman J R
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco 94143-0446.
CONTRACT NUMBER: GM 36426 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Mar 1) 89 (5) 1685-9.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M83772
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 19920424
Last Updated on STN: 19960719
Entered Medline: 19920407

AB Complementary **DNA** (**cDNA**) clones encoding the adult **human liver** flavin-containing monooxygenase (FMO; dimethylaniline N-oxidase, EC 1.14.13.8) were isolated from lambda gt10 and lambda gt11 libraries. The **cDNA** libraries were screened with three synthetic 36-mer oligonucleotide probes derived from the **nucleic** acid sequence of the pig **liver** FMO **cDNA**. The deduced amino acid sequence for the adult **human liver** FMO was quite distinct from the pig **liver** FMO, and adult **human liver** FMO was designated form II (HLFMO II). The full-length **cDNA** sequence of HLFMO II [2119 base pairs (bp)] had an open reading frame of 1599 nucleotides, which encoded a 533-amino acid protein of Mr 59,179, a 5'-noncoding region of 136 nucleotides and a 3'-noncoding region of 369 nucleotides excluding the poly(A) tail. The deduced amino acid sequence of HLFMO II had 80% similarity with the rabbit **liver** FMO II but only a 52%, 55%, and 53% amino acid similarity with the rabbit **liver** (form I), the pig **liver** (form I), and fetal **human liver** (form I) **FMOs**, respectively. **RNA** analysis of adult **human liver RNA** showed that there was one HLFMO II **mRNA** species. Analysis of genomic **DNA** indicated that HLFMO II was the product of a single gene. These results indicated that the deduced amino acid sequence for HLFMO II contained

highly conserved residues and suggested that FMO enzymes were closely related and, undoubtedly, derived from the same ancestral gene.

L13 ANSWER 42 OF 42 MEDLINE DUPLICATE 33
ACCESSION NUMBER: 93038564 MEDLINE
DOCUMENT NUMBER: 93038564 PubMed ID: 1417778
TITLE: Cloning, primary sequence and chromosomal localization of **human** FMO2, a new member of the flavin-containing mono-oxygenase family.
AUTHOR: Dolphin C T; Shephard E A; Povey S; Smith R L; Phillips I R
CORPORATE SOURCE: Department of Biochemistry, Queen Mary & Westfield College, University of London, U.K.
SOURCE: BIOCHEMICAL JOURNAL, (1992 Oct 1) 287 (Pt 1) 261-7.
Journal code: 9YO; 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-M86481; GENBANK-X65728; GENBANK-X65729; GENBANK-X65730; GENBANK-X65731; GENBANK-X65732; GENBANK-X65733; GENBANK-X65734; GENBANK-X66140; GENBANK-Z11737
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19930122
Entered Medline: 19921110

AB We have previously reported the cloning of cDNAs for a flavin-containing mono-oxygenase (FMO) of man, designated FMO1 [Dolphin, Shephard, Povey, Palmer, Ziegler, Ayesh, Smith & Phillips (1991) J. Biol. Chem. 266, 12379-12385], that is the orthologue of pig and rabbit hepatic **FMOs**. We now describe the isolation and characterization of **cDNA** clones for a second **human** FMO, which we have designated FMO2. The polypeptide encoded by the cDNAs is 558 amino acid residues long, has a calculated M(r) of 63337, and contains putative FAD- and NADP-binding sites that align exactly with those described in other mammalian **FMOs**. **Human** FMO2 has 51-53% primary sequence identity with **human** FMO1, rabbit pulmonary FMO and rabbit **liver** FMO form 2, and thus represents a fourth, distinct, member of the mammalian FMO family. The corresponding **mRNA** is present in low abundance in adult **human liver**. Southern blot hybridization with single-exon probes demonstrated that **human** FMO2 and FMO1 are the products of single genes. The gene encoding FMO2 (designated FMO2) was mapped, by the polymerase chain reaction, to **human** chromosome 1, the same chromosome on which FMO1 is located.

09/583,310 Search Strategy/Results

UESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 3 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001165255 MEDLINE
DOCUMENT NUMBER: 21163847 PubMed ID: 11266081
TITLE: A novel deletion in the flavin-containing **monooxygenase** gene (FMO3) in a Greek patient with trimethylaminuria.
AUTHOR: Forrest S M; Knight M; Akerman B R; Cashman J R; Treacy E P
CORPORATE SOURCE: Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia.. forrest@cryptic.rch.unimelb.edu.au
CONTRACT NUMBER: GM36426 (NIGMS)
SOURCE: PHARMACOGENETICS, (2001 Mar) 11 (2) 169-74.
Journal code: BRT; 9211735. ISSN: 0960-314X.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614
AB Mutations of the flavin-containing **monooxygenase type** 3 gene (FMO3) that encode the major functional form present in adult **human liver**, have been shown to cause trimethylaminuria. We now report a novel homozygous deletion of exons 1 and 2 in an Australian of Greek ancestry with TMAuria, the first report of a deletion causative of trimethylaminuria. The deletion occurs 328 bp upstream from exon 1. The 3'-end of the deletion occurs in intron 2, 10013 base pairs downstream from the end of exon 2. The deletion is 12226 bp long. For the proband homozygous for the **human** FMO3 gene deletion, it is predicted that in addition to loss of **monooxygenase** function for **human** FMO3 substrates, such as TMA and other amines, the proband will exhibit decreased tolerance of biogenic amines, both medicinal and those found in foods.

L5 ANSWER 2 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95263022 EMBASE
DOCUMENT NUMBER: 1995263022
TITLE: Sequences promoting the transcription of the **human** XA gene overlapping P450c21A correctly predict the presence of a novel, adrenal-specific, truncated form of tenascin-X.
AUTHOR: Meng Kian Tee; Thomson A.A.; Bristow J.; Miller W.L.
CORPORATE SOURCE: Department of Pediatrics, Bldg. MR-IV, University of California,San Francisco, CA 94143-0978, United States
SOURCE: Genomics, (1995) 28/2 (171-178).
ISSN: 0888-7543 CODEN: GNMCEP
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A compact region in the **human** class III major histocompatibility locus contains the **human** genes for the fourth component of **human** complement (C4) and steroid 21-hydroxylase (P450c21) in one transcriptional orientation, while the gene for the extracellular matrix protein tenascin-X (TN-X) overlaps the last exon of P450c21 on the opposite strand of DNA in the opposite transcriptional orientation. This complex locus is duplicated into A and B loci, so that the organization is 5'-C4A-21A-XA-C4B-21B-XB-3'. Although this duplication event truncated the 65-kb X(B) gene to a 4.5-kb XA gene, the XA gene is transcriptionally active in the adrenal cortex. To examine the basis of the tissue-specific expression of XA and C4B, we cloned the 1763-bp region that lies between the cap sites for XA and C4B and analyzed its promoter activity in both the XA and the C4 orientations. Powerful, **liver**- specific sequences lie within the first 75 to 138 bp from the C4B cap site, and weaker elements lie within 128 bp of the XA cap site that function in both **liver** and adrenal cells. Because these 128 bp upstream from the XA cap site are perfectly preserved in the XB gene encoding TN-X, we sought to determine whether a transcript similar to XA arises within the XB gene. RNase protection assays, cDNA cloning, and RT/PCR show that adrenal cells contain a novel transcript, termed short XB (XB-S), which has the same open reading frame as TN-X. Cell-free translation and immunoblotting show that this transcript encodes a novel 74-kDa XB-S protein that is identical to the carboxy-terminal 673 residues of TN-X. Because this protein consists solely of fibronectin **type III** repeats and a

fibrinogen-like domain, it appears to correspond to an evolutionary precursor of the tenascin family of extracellular matrix proteins.

L5 ANSWER 3 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92104186 EMBASE
DOCUMENT NUMBER: 1992104186
TITLE: Interleukin-1, platelet derived growth factor, free radicals and monocyte aryl hydrocarbon hydroxylase activity in **liver** disease. Role of cell communication.
AUTHOR: Peterson T.C.
CORPORATE SOURCE: Clinical Research Centre, Dalhousie University,Halifax, NS B3H 4H7, Canada
SOURCE: Biochemical Pharmacology, (1992) 43/5 (1163-1166).
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
048 Gastroenterology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Monocytes were isolated from blood of **human** origin and cultured in supplemented leibovitz (L-15) medium for 24 hr. The medium was then decanted and filtered, and all subsequent tests were done on monocyte conditioned medium (MCM). The monocytes of patients with **liver** disease spontaneously secrete temperature-sensitive arylhydrocarbon hydroxylase (AHH) inhibitory factors detectable in the MCM. Anti-interleukin-1 antibody (IL-1Ab) reduced the AHH inhibitory activity of the MCM, suggesting that part of the AHH inhibitory activity was due to interleukin-1 (IL-1). Platelet derived growth factor did not affect AHH activity. Interleukin-1.beta. was detectable in MCM but did not differ significantly between patients and normal volunteers. A time course experiment indicated that interleukin-1.beta. inhibited hepatocyte AHH activity after only 2 hr of incubation. Catalase partially blocked the AHH inhibitory activity of MCM suggesting that activated oxygen intermediates are partially involved in the AHH inhibitory activity of the MCM. Simultaneous incubation of interleukin-1.beta. and catalase did not prevent or augment the inhibitory action of IL-1 on AHH activity. IL-1 stimulates collagen synthesis and elevates serum procollagen **type** 3 peptide (P-III-P). Results indicated that serum P-III-P was elevated in blood sources producing temperature-sensitive AHH inhibitory factor.

=> d 1- ibib abs
YOU HAVE REQUESTED DATA FROM 20 ANSWERS - CONTINUE? Y/(N):y

L15 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:250568 CAPLUS
DOCUMENT NUMBER: 135:302281
TITLE: A novel deletion in the flavin-containing **monooxygenase** gene (FMO3) in a Greek patient with trimethylaminuria
AUTHOR(S): Forrest, Susan M.; Knight, Melanie; Akerman, Beverley R.; **Cashman, John R.**; Treacy, Eileen P.
CORPORATE SOURCE: Murdoch Children's Research Institute, Department of Paediatrics, Royal Children's Hospital, University of Melbourne, Parkville, 3052, Australia
SOURCE: Pharmacogenetics (2001), 11(2), 169-174
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations of the flavin-contg. **monooxygenase** type 3 gene (FMO3) that encode the major functional form present in adult **human liver**, have been shown to cause trimethylaminuria. We now report a novel homozygous deletion of exons 1 and 2 in an Australian of Greek ancestry with TMAuria, the first report of a deletion causative of trimethylaminuria. The deletion occurs 328 bp upstream from exon 1. The 3'-end of the deletion occurs in intron 2, 10013 base pairs downstream from the end of exon 2. The deletion is 12226 bp long. For the proband homozygous for the **human** FMO3 gene deletion, it is predicted that in addn. to loss of **monooxygenase** function for **human** FMO3 substrates, such as TMA and other amines, the proband will exhibit decreased tolerance of biogenic amines, both medicinal and those found in foods.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:645652 CAPLUS
DOCUMENT NUMBER: 127:315640
TITLE: N-oxygenation of phenethylamine to the trans-oxime by adult **human liver** flavin-containing **monooxygenase** and retroreduction of phenethylamine hydroxylamine by **human liver** microsomes
AUTHOR(S): Lin, Jing; **Cashman, John R.**
CORPORATE SOURCE: Seattle Biomedical Research Institute, Seattle, WA, USA
SOURCE: J. Pharmacol. Exp. Ther. (1997), 282(3), 1269-1279
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The biogenic amine phenethylamine has been shown to be N-oxygenated by **human** flavin-contg. **monooxygenase** (FMO) (form 3) and **human liver** microsomes and, to a much lesser extent, N-oxygenated by porcine **liver** FMO1 and porcine **liver** microsomes but not by rabbit FMO2. Adult **human liver** microsomes catalyze the NADPH-dependent N-oxygenation of phenethylamine to the corresponding trans-oxime through the intermediacy of phenethyl hydroxylamine. In addn. to trans-oxime formation, phenethyl hydroxylamine is retroreduced to phenethylamine in the presence of **human** or porcine **liver** microsomes. Studies on the biochem. mechanism of N-oxygenation suggested that trans-oxime formation was dependent on the **human** FMO (form 3) and that retroredn. was stimulated by superoxide and dependent on a cytochrome P 450 system. These conclusions are based on studies examg. the effects of incubation conditions on phenethylamine N-oxygenation and the effect of reactive oxygen species on phenethyl hydroxylamine retroredn., resp. The pharmacol. activity of synthetic phenethyl hydroxylamine and phenethyl oxime with a no. of biogenic amine receptors and transporters was examd. in vitro. In all cases examd., the affinity of phenethyl hydroxylamine and the corresponding oxime for a biogenic transporter or receptors was very poor. The results suggest that the biogenic amine phenethylamine is efficiently sequentially N-oxygenated in the presence of **human liver** microsomes or cDNA-expressed FMO (form 3) to phenethyl hydroxylamine and then to oximes that are pharmacol. inactive and serve to terminate biol. activity. N-oxygenation of phenethylamine to the corresponding trans-oxime is a detoxication process that abrogates pharmacol. activity.

L15 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:545511 CAPLUS
DOCUMENT NUMBER: 127:231026
TITLE: Characterization of two **human** flavin-containing **monooxygenase** (from 3) enzymes expressed in Escherichia coli as maltose binding protein fusions
AUTHOR(S): Brunelle, Alan; Bi, Yi-An; Lin, Jing; Russell, Brett; Luy, Lisa; Berkman, Clifford; **Cashman, John**
CORPORATE SOURCE: Seattle Biomedical Research Institute, Seattle, WA, 98109-1651, USA
SOURCE: Drug Metab. Dispos. (1997), 25(8), 1001-1007
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To examine the possibility for drug metab. polymorphism, adult **human** flavin-contg. monooxygenases (form 3) (EC 1.14.13.8) that differ at one amino acid were expressed in Escherichia coli as maltose binding protein fusions. The cDNA that was first reported during the cloning of adult **human** flavin-contg. **monooxygenase** was designated the wild type lys158 enzyme. A second cDNA has been identified as a common polymorphism in some **human** populations and was designated the glu158 enzyme. The cDNA that encodes both enzymes was subcloned into a high yield protein fusion expression system, expressed, and the protein was partially purified by affinity chromatog. and characterized for enzyme activity with selective functional substrate probes. N-and S-oxygenation activity of both enzymes was detd. with 10-(N,N-dimethylaminopentyl)-2-(trifluoromethyl)phenothiazine and Me p-tolyl sulfide, resp. It was found that expression of both lys158 and glu158 enzymes of the **human** flavin-contg. **monooxygenase** form 3 as fusions with the maltose binding protein resulted in an enzyme that was sol. and greatly stabilized and had a reduced requirement for detergent during enzyme purifn. and during the assay for activity. Expression of the fusion proteins has allowed the prepn. of stable and highly active enzyme at greater purity than was readily possible in the past. With the exception of the stability and soly. characteristics, the phys. and chem. properties of lys158 and glu158 maltose binding fusion proteins of **human** flavin-contg. **monooxygenase** form 3 variants resembled that of flavin-contg. **monooxygenase** enzyme activity assocd. with **human liver** microsomes and enzyme isolated from a previous Escherichia coli expression system that lacked the protein fusion. Comparison of the catalytic activity of the two fusion proteins showed that while both forms were active, there were differences in their substrate specificities. Expression of the adult **human** flavin-contg. **monooxygenase** form 3 as a maltose binding protein has allowed considerable advances over the previously reported cDNA-expressed enzyme systems and may provide the basis for examg. the role of the flavin-contg. **monooxygenase** in **human** xenobiotic or drug metab.

L15 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:476104 CAPLUS
DOCUMENT NUMBER: 127:133707
TITLE: Detoxication of Tyramine by the Flavin-Containing **Monooxygenase**: Stereoselective Formation of the Trans Oxime
AUTHOR(S): Lin, Jing; **Cashman, John R.**
CORPORATE SOURCE: Seattle Biomedical Research Institute, Seattle, WA, 98109, USA
SOURCE: Chem. Res. Toxicol. (1997), 10(8), 842-852
CODEN: CRTOEC; ISSN: 0893-228X
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the presence of pig or adult **human liver** microsomes, tyramine was metabolized to the corresponding trans oxime through the intermediacy of the hydroxylamine. The requisite intermediate, (4-hydroxyphenethyl)hydroxylamine, was retroreduced to tyramine or converted stereoselectively to the trans oxime in the presence of pig or adult **human liver** microsomes. Studies of the effect of metabolic inhibitors suggested that formation of the trans oxime and retroredn. of the hydroxylamine were largely dependent on NADPH and the flavin-contg. **monooxygenase** (FMO) and cytochrome P 450, resp. The conclusion that FMO was predominantly responsible for trans oxime formation in **human liver** microsomes was based on the effect of incubation conditions on tyramine N-oxygenation and the

observation that cDNA-expressed **human** FMO3 also N-oxygenated tyramine to give exclusively the trans oxime. The synthetic hydroxylamine and oxime metabolites of tyramine were examd. for affinity to **human** and animal dopamine and serotonin receptors and the **human** dopamine transporter. For all of the receptors and for the transporter examd., the avidity of the hydroxylamine and oximes was greater than 10 .mu.M and beyond the effective concn. for physiol. relevance. The results suggested that tyramine was sequentially N-oxygenated in the presence of pig and **human liver** microsomes and cDNA-expressed FMO3 to the hydroxylamine and then to the di-N-hydroxylamine that was spontaneously dehydrated to the trans oxime. This may be facilitated by FMO through a nondissociative substrate-enzyme interaction. Based on the biogenic amine receptor or transporter affinity for the hydroxylamine and oxime metabolites of tyramine, N-oxygenation of tyramine by pig or **human liver** FMO may represent a detoxication reaction that terminates the pharmacol. activity of tyramine.

L15 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:619254 CAPLUS
DOCUMENT NUMBER: 126:27762
TITLE: N-Oxygenation of Primary Amines and Hydroxylamines and Retroreduction of Hydroxylamines by Adult **Human Liver** Microsomes and Adult **Human** Flavin-Containing **Monooxygenase** 3
AUTHOR(S): Lin, Jing; Berkman, Clifford E.; **Cashman, John R.**
CORPORATE SOURCE: Seattle Biomedical Research Institute, Seattle, WA, 98108, USA
SOURCE: Chem. Res. Toxicol. (1996), 9(7), 1183-1193
CODEN: CRTOEC; ISSN: 0893-228X
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adult **human liver** microsomes catalyze the NADPH-dependent N-oxygenation of 10-N-(8-aminooctyl)-2-(trifluoromethyl)phenothiazine to the corresponding oximes through the intermediacy of the hydroxylamine. In the presence of adult **human liver** microsomes, the primary amine is stereoselectively converted to the cis-oxime, but addn. of the alternative competitive substrate hydroxylamine hydrochloride apparently decreases the amt. of aliph. hydroxylamine retro-redn. because an increase in oxime formation was obsd. In the presence of hydroxylamine hydrochloride, however, the oxime product recovered was formed with very low stereoselectivity. Studies on the biochem. mechanism of oxime formation suggested that cis-oxime formation in the presence of adult **human liver** microsomes was largely dependent on the **human** flavin-contg. **monooxygenase** (form 3). This conclusion is based on the effects of incubation conditions on product formation when compared to results obsd. in the presence of cDNA-expressed **human** FMO3. The retroredn. of the intermediate hydroxylamine was dependent on NADPH but was not catalyzed by **human** flavin-contg. **monooxygenase** (form 3) or any one of seven prominent cytochromes P 450 that have been well-characterized in the **human liver** microsomes examd. The results suggest that aliph. primary amines are efficiently sequentially N-oxygenated in the presence of **human liver** microsomes to hydroxylamines and then to oximes mainly by the **human** flavin-contg. **monooxygenase**. Retroredn. of the intermediate hydroxylamine is apparently facilitated by a novel but as yet poorly characterized enzyme system that does not employ any of the currently known well-characterized cytochrome P 450 enzymes present in adult **human liver** microsomes.

L15 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:34513 CAPLUS
DOCUMENT NUMBER: 124:169246
TITLE: Molecular cloning of the flavin-containing **monooxygenase** (form II) cDNA from adult **human liver**. [Erratum to document cited in CA118:186740]
AUTHOR(S): Lomri, Noureddine; Gu, Qimin; **Cashman, John R.**
CORPORATE SOURCE: School Pharm, University California, San Francisco, CA, 94143-0446, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(21), 9910
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal

LANGUAGE: English
AB The errors were not reflected in the abstr. or the index entries.

L15 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:895749 CAPLUS
DOCUMENT NUMBER: 123:329208
TITLE: In vitro hepatic metabolism of ABT-418 in chimpanzee (Pan troglodytes): a unique pattern of microsomal flavin-containing **monooxygenase**-dependent stereoselective N'-oxidation
AUTHOR(S): Rodrigues, A. David; Kukulka, Michael J.; Ferrero, James L.; **Cashman, John R.**
CORPORATE SOURCE: Drug Metabolism Department, Abbott Laboratories, Abbott Park, IL, 60064-3500, USA
SOURCE: Drug Metab. Dispos. (1995), 23(10), 1143-52
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Metab. of the cholinergic channel activator [N-methyl-3H]ABT-418 was studied using precision-cut tissue slices and microsomes (.+-.cytosol) prepd. from a single chimpanzee **liver**. In both cases, the products of C-oxidn. (lactam) and N'-oxidn. (cis > trans) were detected. In the presence of chimpanzee **liver** microsomes and cytosol, which had been characterized with respect to the levels of aldehyde oxidase (N1-methylnicotinamide oxidase), NADPH-dependent flavin-contg. **monooxygenase** (FMO; N,N-dimethylaniline N-oxidase), and various cytochrome P 450 (CYP)-dependent **monooxygenase** activities, ABT-418 lactam and N'-oxide formation was largely dependent on CYP/aldehyde oxidase and FMO, resp. The rank order of total (trans + cis) FMO-dependent N'-oxidn. in **liver** microsomes was dog > rat > rabbit > chimpanzee .gtoreq. cynomolgus monkey > **human**. It is concluded that the metabolic profile of ABT-418 in the chimpanzee is unique. First, the C-/N'-oxidn. ratio in **liver** slices (0.43) is similar to that of the rat and dog and dissimilar to that of the two other primate species studied; **human** and cynomolgus monkey (C-/N'-oxidn. ratio .gtoreq. 9.4). Second, the pattern of ABT-418 N'-oxidn. obsd. with chimpanzee **liver** microsomes, and **liver** slices (trans:cis = 1:3), differs from that of rat, rabbit, and dog **liver** microsomes, rat and **human** kidney S-9 (trans .mchgt. cis), **human liver** microsomes (trans:cis .apprx. 1:1), and cynomolgus monkey (trans:cis .apprx. 2:1) **liver** microsomes. Lack of stereoselective N'-oxidn. by **human** FMO was confirmed with cDNA-expressed FMO3.

L15 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:874565 CAPLUS
TITLE: Molecular cloning of the flavin-containing **monooxygenase** (form II) cDNA from adult **human liver**
AUTHOR(S): Lomri, N.; Gu, Q.; **Cashman, J. R.**
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1995), 92(21), 9910
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal; Errata
LANGUAGE: English
AB Unavailable

L15 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:758120 CAPLUS
DOCUMENT NUMBER: 123:163167
TITLE: In vitro-in vivo correlations of **human** (S)-nicotine metabolism
AUTHOR(S): Berkman, Clifford E.; Park, Sang B.; Wrighton, Steven A.; **Cashman, John R.**
CORPORATE SOURCE: Seattle Biomedical Research Institute, Seattle, WA, 98109, USA
SOURCE: Biochem. Pharmacol. (1995), 50(4), 565-70
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The profile of (S)-nicotine metab. in **human liver** microsomes was examd. at concns. approaching in vivo conditions (10 .mu.M). At such concns., no (S)-nicotine N-1'-oxygenation was seen, and thus C-oxidn. to the (S)-nicotine .DELTA.1',5'-iminium ion was the sole product obsd. in the metabolic profile in the presence of the **human liver** microsomes. For simplicity of anal., the (S)-nicotine .DELTA.1',5'-iminium ion formed was converted to (S)-cotinine in the presence of exogenously added aldehyde oxidase. To explain the lack of (S)-nicotine N-1'-oxygenation at low (S)-nicotine concns.,

inhibition of flavin-contg. **monooxygenase** (FMO) activity by (S)-cotinine was examd. Although (S)-cotinine was obsd. to inhibit pig FMO1 (Ki = 675 .mu.M), partially purified cDNA-expressed adult **human liver** FMO3 was not inhibited by (S)-cotinine. The authors therefore concluded that the kinetic properties of the nicotine N'- and C-oxidases were responsible for the metabolic product profile obsd. Kinetic consts. were detd. for individual **human liver** microsomal prepns. from low (10 .mu.M) and high (500 .mu.M) (S)-nicotine concns. by monitoring (S)-cotinine formation with HPLC. The mean Kmapp and Vmax for formation of (S)-cotinine by the microsomes examd. were 39.6 .mu.M and 444.3 pmol.cntdot.min-1.(mg protein)-1, resp. The formation of (S)-cotinine was strongly dependent on the previous drug administration history of each subject, and among the highest rates for (S)-cotinine formation were those of the barbiturate-pretreated subjects. The rate of (S)-cotinine formation at low (10 .mu.M) concn. correlated well with immunoreactivity for cytochrome P 450 2A6 (r = 0.89). In vitro-in vivo correlation of the results suggests that the low amt. of (S)-nicotine N-1'-oxygenation and the large amt. of (S)-cotinine formed in **human** smokers (i.e. 4 and 30% of a typical dose, resp.) are detd. primarily by the kinetic properties of the **human monooxygenase** enzyme systems. However, addnl. non-hepatic **monooxygenase**(s) contributes to (S)-nicotine metab.

L15 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:495570 CAPLUS
DOCUMENT NUMBER: 122:281214
TITLE: Role of hepatic flavin-containing **monooxygenase** 3 in drug and chemical metabolism in adult humans
AUTHOR(S): **Cashman, John R.**; Park, Sang B.; Berkman, Clifford E.; Cashman, Lisa E
CORPORATE SOURCE: Seattle Biomedical Research Institute, 4 Nickerson Street, Suite 200, Seattle, WA, 98109, USA
SOURCE: Chem.-Biol. Interact. (1995), 96(1), 33-46
CODEN: CBINA8; ISSN: 0009-2797
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 55 refs. In conjunction with asym. chem. syntheses and spectral, chiroptical, chromatog. and stereochem. correlation methods, the authors have developed procedures for the quantification of sulfoxide enantiomers and tertiary amine N-oxide diastereomer metabolites arising from the action of the adult **human liver** and other flavin-contg. monooxygenases (FMOs). The parallel nature of the metabolic in vitro-in vivo studies and the use of chem. model oxidn. systems allowed the authors to identify the FMO isoform involved. The authors investigated the enantioselective S-monooxygenation of cimetidine and the diastereoselective tertiary amine N-1'-oxygenation of (S)-nicotine as stereoselective functional probes of adult **human liver** FMO action. In both cases, the majority of evidence points to adult **human liver** FMO3 as the principal enzyme responsible for cimetidine S-oxygenation and (S)-nicotine N-1'-oxygenation in vitro and in vivo. The excellent agreement between the abs. configuration of the major cimetidine S-oxide and (S)-nicotine N-1'-oxide metabolites isolated from **human** urine and the major metabolite formed in the presence of adult **human liver** microsomes suggests that in vitro hepatic prepns. may serve as a useful model for the in vivo condition. Further, that adult **human liver** cDNA-expressed FMO3 in Escherichia coli also gave the same abs. stereoselectivity (i.e. for (S)-nicotine N-1'-oxygenation) confirms the identity of the **monooxygenase** in vivo. Although the authors cannot rule out the involvement of minor contributions of cytochrome P 450 monooxygenases in cimetidine and (S)-nicotine oxidn., the majority of the data support the fact that cimetidine S-oxygenation and (S)-nicotine N-1'-oxygenation are stereoselective functional probes of adult **human liver** FMO3 activity. Finally, because the stereochem. of the principal metabolite of cimetidine and (S)-nicotine in small exptl. animals is distinct from that obsd. in humans, it is likely that species variation in predominant FMO isoforms exist and this may have important consequences for the choice of exptl. animals in **human** preclin. drug design and development programs.

L15 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:207839 CAPLUS
DOCUMENT NUMBER: 120:207839
TITLE: Stereo- and regioselective N- and S-oxidation of tertiary amines and sulfides in the presence of adult **human liver** microsomes. [Erratum to document cited in CA119(11):108339g]

AUTHOR(S): **Cashman, John R.**; Yang, Zicheng; Wang, Lihong; Wrighton, Steven A.
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, USA
SOURCE: Drug Metab. Dispos. (1993), 21(6), 1174
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The errors were not reflected in the abstr. or the index entries.

L15 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:92 CAPLUS
DOCUMENT NUMBER: 120:92
TITLE: Comparison of **human** and rhesus monkey in vitro phase I and phase II hepatic drug metabolism activities
AUTHOR(S): Stevens, Jeffrey; Shipley, Lisa A.; **Cashman, John R.**; Vandenbranden, Mark; Wrighton, Steven A.
CORPORATE SOURCE: Dep. Drug Metab. Disposit., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Drug Metab. Dispos. (1993), 21(5), 753-60
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Twelve **human** and six rhesus monkey **liver** samples were analyzed in vitro for phase I metab. and phase II conjugation activity. Of the eight P 450-dependent activities measured, only N-nitrosodimethylamine N-demethylase activity was not significantly different between the two species. Coumarin 7-hydroxylase activity was greater in the **human** as compared with the rhesus monkey samples, whereas erythromycin N-demethylase, benzphetamine N-demethylase, pentoxyresorufin O-dealkylase, ethoxycoumarin O-deethylase, and ethoxyresorufin O-deethylase activities were significantly greater in rhesus monkey microsome samples. Cimetidine S-oxygenation and chlorpromazine N-oxygenation were 2.1- and 2.6-fold higher in rhesus monkey samples. Of the seven microsomal and cytosolic phase II activities measured, only 17.alpha.-ethylnylestradiol glucuronidation was significantly higher in the **human** samples. The genetic polymorphism for isoniazid acetylation was evident only in the **human** samples, with activities varying 200-fold. This study shows that, although the rhesus monkey is often used by the pharmaceutical industry as a representative mammalian species for drug testing, the in vitro metabolic capabilities of the **human** and rhesus monkey drug metabolizing enzymes are different.

L15 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:664287 CAPLUS
DOCUMENT NUMBER: 119:264287
TITLE: Regio- and stereoselective oxygenations by adult **human liver** flavin-containing **monooxygenase** 3. Comparison with forms 1 and 2
AUTHOR(S): Lomri, Noureddine; Yang, Zicheng; **Cashman, John R.**
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA
SOURCE: Chem. Res. Toxicol. (1993), 6(6), 800-7
CODEN: CRTOEC; ISSN: 0893-228X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cDNA for the adult **human liver** flavin-contg. **monooxygenase** (form 3) (FMO3) was cloned, sequenced, and expressed in Escherichia coli. The cDNA-expressed FMO3 was used to investigate the regio- and stereoselective N- and S-oxygenation of a no. of tertiary amines and sulfides, resp. For comparison, the N- and S-oxygenation of the same chems. and drugs were examd. with adult **human liver** microsomes from a normal healthy female donor and FMO1 from pig **liver** and FMO2 from rabbit lung. Both cDNA-expressed FMO3 and adult **human liver** microsomes N-oxygenated trifluoperazine or 10-(N,N-dimethylaminoalkyl)-phenothiazines with similar substrate specificities. The substrate specificity for FMO3 differed, however, from that of pig **liver** FMO1. Nucleophilic sulfur-contg. compds. [i.e., thiobenzamide, (4-bromophenyl)-1,3-oxathiolane, and 2-methyl-1,3-benzodithiole] were efficiently S-oxygenated by cDNA-expressed FMO3 and adult **human liver** microsomes. Stereoselective S-oxygenation of (+)- and (-)-(4-bromophenyl)-1,3-oxathiolane and 2-methyl-1,3-benzodithiole was therefore investigated. In general, the stereoselectivity obsd. for S-oxygenation in the presence of FMO3 was similar to that obsd. in the presence of adult **human liver** microsomes. In most

cases examd., however, the stereoselectivity for S-oxygenation was quite distinct from that obsd. for pig **liver** FMO1. The authors conclude that FMO3 is the major form of FMO active in adult **human liver**. Because the stereoselectivity for S-oxygenation and the substrate specificity for tertiary amine N-oxygenation by cDNA-expressed FMO3 are distinct from those of pig **liver** FMO1, the authors conclude that the binding channel for each isoform is quite different. Like FMO2 from rabbit lung, FMO3 apparently possesses a much smaller substrate binding channel than pig **liver** FMO1, and this undoubtedly has consequences for tertiary amine and sulfide metab. in humans.

L15 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:661944 CAPLUS
DOCUMENT NUMBER: 119:261944
TITLE: Chemical, enzymic, and **human** enantioselective S-oxygenation of cimetidine
AUTHOR(S): **Cashman, John R.**; Park, Sang B.; Yang, Zi Chen; Washington, Carla B.; Gomez, Denise Y.; Giacomini, Kathleen M.; Brett, Claire M.
CORPORATE SOURCE: Dep. Pharm. Chem., Univ. California, San Francisco, CA, USA
SOURCE: Drug Metab. Dispos. (1993), 21(4), 587-97
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The S-oxygenation of cimetidine was investigated using achiral chem. and chiral chem. and enzymic S-oxygenation procedures. The products of the reactions were thoroughly characterized by spectral, chiroptical, chromatog., and stereochem. correlation methods. S-Oxygenation by the Kagan method or in the presence of pig **liver** microsomes or pig **liver** flavin-contg. **monooxygenase** (FMO) (form I) all gave essentially identical enantioselectivity: the av. enantiomeric excess was -13.4% and the stereopreference was for formation of (+)-cimetidine S-oxide in a ratio of (+)56.7%:(-)43.3%. The profile of immunoreactivity and the effect of metab. inhibitors on cimetidine S-oxide formation in the presence of pig **liver** microsomes were consistent with a role of FMO (form I) in enantioselective (+)-cimetidine S-oxide formation. Administration of cimetidine to seven healthy male volunteers provided pharmacokinetic parameters for cimetidine and cimetidine S-oxide that were typical of those for previously reported studies. The urinary cimetidine S-oxide was isolated and the stereopreference was for formation of (-)-cimetidine S-oxide in a ratio of (+)25.5%:(-)74.5%. In good agreement with the enantiomeric enrichment values obsd. for the adult **human** urinary metabolite, the relative configuration of cimetidine S-oxide formed in adult **human liver** microsomes was (+)-15.8%:(-)-84.2%. Because of the enantioselectivity and profile of immunoreactivity and the effect of metab. inhibitors on cimetidine S-oxygenation in adult **human liver** microsomes are consistent with a role of FMO (form II) in cimetidine S-oxide formation and because the enantioselectivity of cimetidine S-oxide obsd. in adult humans is similar, the authors conclude that in vivo, cimetidine is S-oxygenated principally by FMO (form II).

L15 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:643495 CAPLUS
DOCUMENT NUMBER: 119:243495
TITLE: Stereoselective metabolism of (S)-(-)-nicotine in humans: Formation of trans-(S)-(-)-nicotine N-1'-oxide
AUTHOR(S): Park, Sang B.; Jacob, Peyton, III; Benowitz, Neal L.; **Cashman, John R.**
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA
SOURCE: Chem. Res. Toxicol. (1993), 6(6), 880-8
CODEN: CRTOEC; ISSN: 0893-228X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The metab. of (S)-nicotine was investigated in the presence of microsomes, cDNA-expressed and highly purified flavin-contg. **monooxygenase** (FMO) from pig **liver**, **human liver**, and rabbit lung. For comparison, the N-1'-oxidn. of (S)-nicotine in the presence of the cytochrome P 450 2B1 from rat **liver**, cytochrome P 450 2B10 from mouse **liver**, and cytochrome P 450 4A2 from rabbit lung was examd. The ratio of trans:cis (S)-nicotine N-1'-oxide formation for pig **liver** FMO (form 1) was 57:43. In contrast, cDNA-expressed adult **human liver** FMO (form 3) and rabbit lung FMO2 formed solely trans (S)-nicotine N-1'-oxide. Of the

cytochrome P 450 enzymes examd., formation of (S)-nicotine N-1'-oxide occurred with a mean trans:cis ratio of 82:18. The stereoselectivity of (S)-nicotine N-1'-oxide formation was investigated by examg. the urine of 13 healthy male smokers studied on a protocol which included free-smoking, i.v. infusion of (S)-nicotine-d2 and dermal patch administration of (S)-nicotine-d0. During cigarette smoking or administration of i.v. or transdermal (S)-nicotine, only the trans diastereomer of (S)-nicotine N-1'-oxide was obsd. in the urine. That the trans (S)-nicotine N-1'-oxide metabolite was not appreciably reduced or oxidized further was investigated with infusion studies of (S)-nicotine-d2 N-1'-oxide. The mean trans:cis (S)-nicotine N-1'-oxide ratio detd. from the metabolite isolated from the urine of humans after infusion of the N-1'-oxide was 60:40, which was essentially identical to that of the infusate. Previously, the authors have obsd. exclusive trans-(S)-nicotine N-1'-oxide formation in the presence of 14 different adult **human liver** microsome samples. As described herein, after administration of (S)-nicotine to 13 healthy adult smokers by 3 different routes of administration, the authors also obsd. only trans-(S)-nicotine N-1'-oxide formation. The excellent agreement between in vitro and in vivo results suggests that **human** (S)-nicotine N-1'-oxygenation is catalyzed predominantly by one **monooxygenase**. The majority of the data strongly suggests that the adult **human liver** flavin-contg. **monooxygenase** (form 3) is responsible for trans-(S)-nicotine N-1'-oxygenation, and the authors propose that formation of this metabolite is a selective functional marker for the enzyme.

L15 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:508339 CAPLUS
DOCUMENT NUMBER: 119:108339
TITLE: Stereo- and regioselective N- and S-oxidation of tertiary amines and sulfides in the presence of adult **human liver** microsomes
AUTHOR(S): **Cashman, John R.**; Yang, Zicheng; Yang, Lihong; Wrighton, Steven A.
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, USA
SOURCE: Drug Metab. Dispos. (1993), 21(3), 492-501
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adult **human liver** microsomes supplemented with NADPH catalyzed the regioselective N-oxygenation of the aliph. tertiary amine and S-oxidn. of the phenothiazine sulfur atom of several 10-(N,N-dimethylaminoalkyl)phenothiazines. In addn., (+)- and (-)-4-bromophenyl-1,3-oxathiolane were converted to the corresponding S-oxides in the presence of NADPH and adult **human liver** microsomes. The (+) and (-) enantiomers of 4-bromophenyl-1,3-oxathiolane were converted to the S-oxides with low and high stereoselectivity, resp. Studies on the biochem. mechanism for N-oxygenation of 10-(N,N-dimethylaminoalkyl)phenothiazines suggested that this reaction was catalyzed by the flavin-contg. **monooxygenase** (form II), although cytochrome P 450 2D6 may also have contributed to N-oxide formation. S-Oxidn. of chlorpromazine was catalyzed mainly by cytochrome P 450, including cytochromes P 450 2A6, 2C8, and 2D6. S-Oxygenation of (+)-4-bromophenyl-1,3-oxathiolane produced a mixt. of the cis- and trans diastereomers in a process probably dependent on both hepatic **monooxygenase** systems. (-)-4-Bromophenyl-1,3-oxathiolane was converted almost exclusively to the trans-S-oxide in a process likely dependent on the adult **human liver** flavin-contg. **monooxygenase** (form II). Development of regio- and stereochem. probes of adult **human liver** flavin-contg. **monooxygenase** (form II) and cytochromes P 450 activity may be useful for eventual in vitro-in vivo correlations, but may require approaches quite distinct from that currently used for animal monooxygenases.

L15 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:466327 CAPLUS
DOCUMENT NUMBER: 119:66327
TITLE: Expression in Escherichia coli of the flavin-containing **monooxygenase** D (form II) from adult **human liver**: Determination of a distinct tertiary amine substrate specificity
AUTHOR(S): Lomri, Noureddine; Yang, Zicheng; **Cashman, John R.**
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA

SOURCE: Chem. Res. Toxicol. (1993), 6(4), 425-9
CODEN: CRTOEC; ISSN: 0893-228X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cDNA for a major component of the family of flavin-contg. monooxygenases (FMOs) present in adult **human liver** (i.e., HLFMO-D) has been cloned and expressed in a prokaryotic system. Escherichia coli strain NM522 was transformed with pTrcHLFMO-D, and the HLFMO-D cDNA was expressed under the control of the Trc promoter. A variety of tertiary amine substrates [i.e., chlorpromazine and 10-[(N,N-dimethylamino)alkyl]-2-(trifluoromethyl)phenothiazines] were efficiently oxygenated by HLFMO-D cDNA expressed in E. coli or by adult **human liver** microsomes. Approx. dimensions of the substrate binding channel for both adult **human liver** microsomal FMO and cDNA-expressed HLFMO-D were apparent from an examn. of the N-oxygenation of a series of 10-[(N,N-dimethylamino)alkyl]-2-(trifluoromethyl)phenothiazines. The substrate regioselectivity studies suggest that adult **human liver** FMO form D possesses a distinct substrate specificity compared with form A FMO from animal hepatic sources. It is likely that the substrate specificity obsd. for cDNA-expressed adult **human liver** FMO-D may have consequences for the metab. and distribution of tertiary amines and phosphorus- and sulfur-contg. drugs in humans and may provide insight into the physiol. substrate(s) for adult **human liver** FMO.

L15 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:186740 CAPLUS
DOCUMENT NUMBER: 118:186740
TITLE: Molecular cloning of the flavin-containing **monooxygenase** (form II) cDNA from adult **human liver**
AUTHOR(S): Lomri, Noureddine; Gu, Qimin; **Cashman, John R.**
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1992), 89(5), 1685-9
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several cDNA clones encoding the adult **human liver** flavin-contg. **monooxygenase** (FMO; dimethylaniline N-oxidase, EC 1.14.13.8) were isolated from .lambda.gt10 and .lambda.gt11 libraries. The cDNA libraries were screened with 3 synthetic 36-mer oligonucleotide probes derived from the nucleic acid sequence of pig **liver** FMO cDNA. The deduced amino acid sequence for adult **human liver** FMO was quite distinct from pig **liver** FMO, and adult **human liver** FMO was designated form II (HLFMO II). The full-length cDNA sequence of HLFMO II [2119 base pairs (bp)] had an open reading frame of 1599 nucleotides, which encoded a 533-amino acid protein of Mr 59,179, a 5'-noncoding region of 136 nucleotides and a 3'-noncoding region of 369 nucleotides, excluding the poly(A) tail. The deduced amino acid sequence of HLFMO II had 80% similarity with the rabbit **liver** FMO II but only 52%, 55%, and 53% amino acid similarity with rabbit **liver** (form I), pig **liver** (form I), and fetal **human liver** (form I) FMOs, resp. RNA anal. of adult **human liver** RNA showed that there was one HLFMO II mRNA species. Anal. of genomic DNA indicated that HLFMO II was the product of a single gene. Thus, the deduced amino acid sequence for HLFMO II contained highly conserved residues and suggested that FMO enzymes were closely related and, undoubtedly, derived from the same ancestral gene.

L15 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:545205 CAPLUS
DOCUMENT NUMBER: 117:145205
TITLE: Metabolism of nicotine by **human liver** microsomes: stereoselective formation of trans-nicotine N'-oxide
AUTHOR(S): **Cashman, John R.**; Park, Sang B.; Yang, Z. C.; Wrighton, Steven A.; Jacob, Peyton, III; Benowitz, Neal L.
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA
SOURCE: Chem. Res. Toxicol. (1992), 5(5), 639-46
CODEN: CRTOEC; ISSN: 0893-228X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Liver** microsomes from humans catalyze the NADPH-dependent oxidn. of (S)-nicotine. The principal product is the 5'-carbon atom oxidn. product, nicotine .DELTA.1',5'-iminium ion, which is efficiently converted

to the .gamma.-lactam deriv. cotinine in the presence of aldehyde oxidase. Another major product is nicotine N'-oxide. In contrast to previous reports, describing in vitro or in vivo studies, formation of only trans-nicotine N'-oxide was obsd. Demethylation of nicotine was not obsd. Studies on the biochem. mechanism of nicotine 5-carbon atom oxidn. strongly implicate one major cytochrome P 450 isoenzyme (i.e., P 450 2A6) as largely responsible for .DELTA.1',5'-iminium ion formation. Stereoselective formation of trans-nicotine N'-oxide may be catalyzed in large part by the flavin-contg. **monooxygenase** (form II). These conclusions are based on the effects of alternative substrates for the flavin-contg. **monooxygenase**, heat inactivation studies, immunoblot studies, and selective substrates for cytochromes P 450. The results suggest that (S)-nicotine trans N'-oxygenation and .DELTA.1',5'-iminium ion formation may be selective probes of **human liver** flavin-contg. **monooxygenase** form II and cytochrome P 450 2A6 activities, resp., useful for in vivo phenotyping of humans.

L15 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1986:179654 CAPLUS
DOCUMENT NUMBER: 104:179654
TITLE: Contribution of N-oxygenation to the metabolism of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) by various **liver** preparations
AUTHOR(S): **Cashman, John R.**; Ziegler, D. M.
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143, USA
SOURCE: Mol. Pharmacol. (1986), 29(2), 163-7
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Liver** microsomes from uninduced mice and rats catalyzed NADPH- and O-dependent N-oxygenation of the neurotoxin (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [28289-54-5]. The N-oxide [95969-40-7] is the principal product and accounts for 95-96% of the total MPTP metabolized by microsomes. Demethylation of MPTP is detectable but the rate of nor-MPTP [10338-69-9] formation is never >4-6% of the rate of N-oxygenation. Studies on the biochem. mechanisms for N-oxygenation of MPTP suggest that this reaction is catalyzed exclusively by the flavin **monooxygenase** [37256-73-8]. This conclusion is based on the effects of selective cytochrome P 450 inhibitors, pos. effectors, and alternate substrates for the flavin-contg. **monooxygenase** as well as on studies with the purified hog **liver** enzyme. MPTP is an excellent substrate for this **monooxygenase** with a Km of 30-33 .mu.M. Limited studies with **human liver** whole homogenates suggest that N-oxygenation is also a major route for the metab. of MPTP in man and the rate of MPTP N-oxide formation is approx. equal to the rate of mitochondrial monoamine oxidase-dependent MPDP+ (1-methyl-4-phenyl-2,3-dihydropyridinium species) prodn.

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=> E LOMRI N/AU 25
E1          13     LOMRI A/AU
E2          26     LOMRI ABDERRAHIM/AU
E3          11 --> LOMRI N/AU
E4           2     LOMRI NOUR EDDINE/AU
E5           1     LOMRI NOURDINE/AU
E6          14     LOMRI NOUREDDINE/AU
E7           6     LOMRI NOURREDINE/AU
E8           2     LOMRY/AU
E9          11     LOMSADZE A V/AU
E10          1     LOMSADZE ALEXANDRE/AU
E11          6     LOMSADZE B/AU
E12         97     LOMSADZE B A/AU
E13          1     LOMSADZE D I/AU
E14          2     LOMSADZE D M/AU
E15         18     LOMSADZE G I/AU
E16          1     LOMSADZE K T/AU
E17          2     LOMSADZE KETEVAN/AU
E18          1     LOMSADZE M SH/AU
E19          1     LOMSADZE N/AU
E20          3     LOMSADZE R/AU
E21          7     LOMSADZE R A/AU
E22          8     LOMSADZE R N/AU
E23          3     LOMSADZE R O/AU
E24          5     LOMSADZE SH YU/AU
E25          2     LOMSADZE T E/AU
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09/583,310 Search Strategy/Results

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=> S (E3 OR E4 OR E5 OR E6 OR E7) AND (MONOOXYGENASE AND LIVER AND HUMAN)
            11 "LOMRI N"/AU
             2 "LOMRI NOUR EDDINE"/AU
             1 "LOMRI NOURDINE"/AU
            14 "LOMRI NOUREDDINE"/AU
             6 "LOMRI NOURREDINE"/AU
         10940 MONOOXYGENASE
        456971 LIVER
        972773 HUMAN
L16          5 ("LOMRI N"/AU OR "LOMRI NOUR EDDINE"/AU OR "LOMRI NOURDINE"/AU OR "LOMRI NOUREDDINE"/AU
OR "LOMRI NOURREDINE"/AU) AND (MONOOXYGENASE AND LIVER AND HUMAN)

=> d 1- ibib abs
YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):y

L16  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        1996:34513  CAPLUS
DOCUMENT NUMBER:         124:169246
TITLE:                   Molecular cloning of the flavin-containing
                         monooxygenase (form II) cDNA from adult
                         human liver. [Erratum to document
                         cited in CA118:186740]
AUTHOR(S):               Lomri, Noureddine; Gu, Qimin; Cashman, John
                         R.
CORPORATE SOURCE:        School Pharm, University California, San Francisco,
                         CA, 94143-0446, USA
SOURCE:                  Proceedings of the National Academy of Sciences of the
                         United States of America (1995), 92(21), 9910
                         CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:               National Academy of Sciences
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The errors were not reflected in the abstr. or the index entries.

L16  ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        1995:874565  CAPLUS
TITLE:                   Molecular cloning of the flavin-containing
                         monooxygenase (form II) cDNA from adult
                         human liver
AUTHOR(S):               Lomri, N.; Gu, Q.; Cashman, J. R.
SOURCE:                  Proc. Natl. Acad. Sci. U. S. A. (1995), 92(21), 9910
                         CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE:           Journal; Errata
LANGUAGE:                English
AB   Unavailable

L16  ANSWER 3 OF 5  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:        1993:664287  CAPLUS
DOCUMENT NUMBER:         119:264287
TITLE:                   Regio- and stereoselective oxygenations by adult
                         human liver flavin-containing
                         monooxygenase 3. Comparison with forms 1 and 2
AUTHOR(S):               Lomri, Noureddine; Yang, Zicheng; Cashman,
                         John R.
CORPORATE SOURCE:        Sch. Pharm., Univ. California, San Francisco, CA,
                         94143-0446, USA
SOURCE:                  Chem. Res. Toxicol. (1993), 6(6), 800-7
                         CODEN: CRTOEC; ISSN: 0893-228X
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The cDNA for the adult human liver flavin-contg.
     monooxygenase (form 3) (FMO3) was cloned, sequenced, and expressed
     in Escherichia coli. The cDNA-expressed FMO3 was used to investigate the
     regio- and stereoselective N- and S-oxygenation of a no. of tertiary
     amines and sulfides, resp. For comparison, the N- and S-oxygenation of
     the same chems. and drugs were examd. with adult human
     liver microsomes from a normal healthy female donor and FMO1 from
     pig liver and FMO2 from rabbit lung. Both cDNA-expressed FMO3
     and adult human liver microsomes N-oxygenated
     trifluoperazine or 10-(N,N-dimethylaminoalkyl)-phenothiazines with similar
     substrate specificities. The substrate specificity for FMO3 differed,
     however, from that of pig liver FMO1. Nucleophilic
     sulfur-contg. compds. [i.e., thiobenzamide, (4-bromophenyl)-1,3-
     oxathiolane, and 2-methyl-1,3-benzodithiole] were efficiently S-oxygenated
     by cDNA-expressed FMO3 and adult human liver
     microsomes. Stereoselective S-oxygenation of (+)- and
     (-)-(4-bromophenyl)-1,3-oxathiolane and 2-methyl-1,3-benzodithiole was
     therefore investigated. In general, the stereoselectivity obsd. for
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S-oxygenation in the presence of FMO3 was similar to that obsd. in the presence of adult **human liver** microsomes. In most cases examd., however, the stereoselectivity for S-oxygenation was quite distinct from that obsd. for pig **liver** FMO1. The authors conclude that FMO3 is the major form of FMO active in adult **human liver**. Because the stereoselectivity for S-oxygenation and the substrate specificity for tertiary amine N-oxygenation by cDNA-expressed FMO3 are distinct from those of pig **liver** FMO1, the authors conclude that the binding channel for each isoform is quite different. Like FMO2 from rabbit lung, FMO3 apparently possesses a much smaller substrate binding channel than pig **liver** FMO1, and this undoubtedly has consequences for tertiary amine and sulfide metab. in humans.

L16 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:466327 CAPLUS
DOCUMENT NUMBER: 119:66327
TITLE: Expression in Escherichia coli of the flavin-containing **monooxygenase** D (form II) from adult **human liver**: Determination of a distinct tertiary amine substrate specificity
AUTHOR(S): **Lomri, Noureddine**; Yang, Zicheng; Cashman, John R.
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA
SOURCE: Chem. Res. Toxicol. (1993), 6(4), 425-9
CODEN: CRTOEC; ISSN: 0893-228X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cDNA for a major component of the family of flavin-contg. monooxygenases (FMOs) present in adult **human liver** (i.e., HLFMO-D) has been cloned and expressed in a prokaryotic system. Escherichia coli strain NM522 was transformed with pTrcHLFMO-D, and the HLFMO-D cDNA was expressed under the control of the Trc promoter. A variety of tertiary amine substrates [i.e., chlorpromazine and 10-[(N,N-dimethylamino)alkyl]-2-(trifluoromethyl)phenothiazines] were efficiently oxygenated by HLFMO-D cDNA expressed in E. coli or by adult **human liver** microsomes. Approx. dimensions of the substrate binding channel for both adult **human liver** microsomal FMO and cDNA-expressed HLFMO-D were apparent from an examn. of the N-oxygenation of a series of 10-[(N,N-dimethylamino)alkyl]-2-(trifluoromethyl)phenothiazines. The substrate regioselectivity studies suggest that adult **human liver** FMO form D possesses a distinct substrate specificity compared with form A FMO from animal hepatic sources. It is likely that the substrate specificity obsd. for cDNA-expressed adult **human liver** FMO-D may have consequences for the metab. and distribution of tertiary amines and phosphorus- and sulfur-contg. drugs in humans and may provide insight into the physiol. substrate(s) for adult **human liver** FMO.

L16 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:186740 CAPLUS
DOCUMENT NUMBER: 118:186740
TITLE: Molecular cloning of the flavin-containing **monooxygenase** (form II) cDNA from adult **human liver**
AUTHOR(S): **Lomri, Noureddine**; Gu, Qimin; Cashman, John R.
CORPORATE SOURCE: Sch. Pharm., Univ. California, San Francisco, CA, 94143-0446, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1992), 89(5), 1685-9
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several cDNA clones encoding the adult **human liver** flavin-contg. **monooxygenase** (FMO; dimethylaniline N-oxidase, EC 1.14.13.8) were isolated from .lambda.gt10 and .lambda.gt11 libraries. The cDNA libraries were screened with 3 synthetic 36-mer oligonucleotide probes derived from the nucleic acid sequence of pig **liver** FMO cDNA. The deduced amino acid sequence for adult **human liver** FMO was quite distinct from pig **liver** FMO, and adult **human liver** FMO was designated form II (HLFMO II). The full-length cDNA sequence of HLFMO II [2119 base pairs (bp)] had an open reading frame of 1599 nucleotides, which encoded a 533-amino acid protein of Mr 59,179, a 5'-noncoding region of 136 nucleotides and a 3'-noncoding region of 369 nucleotides, excluding the poly(A) tail. The deduced amino acid sequence of HLFMO II had 80% similarity with the rabbit

liver FMO II but only 52%, 55%, and 53% amino acid similarity with rabbit **liver** (form I), pig **liver** (form I), and fetal **human liver** (form I) FMOs, resp. RNA anal. of adult **human liver** RNA showed that there was one HLFMO II mRNA species. Anal. of genomic DNA indicated that HLFMO II was the product of a single gene. Thus, the deduced amino acid sequence for HLFMO II contained highly conserved residues and suggested that FMO enzymes were closely related and, undoubtedly, derived from the same ancestral gene.

IUBMB Enzyme Nomenclature

EC 1.14.13.8

Common name: dimethylaniline monooxygenase (*N*-oxide-forming)

Reaction: *N,N*-dimethylaniline + $NADPH_2$ + O_2 = *N,N*-dimethylaniline *N*-oxide + NADP + H_2O

Other name(s): dimethylaniline oxidase; dimethylaniline *N*-oxidase; FAD-containing monooxygenase; *N,N*-dimethylaniline monooxygenase; DMA oxidase; mixed-function amine oxidase; FMO; FMO-I; FMO-II; flavin monooxygenase; flavin-containing monooxygenase

Systematic name: *N,N*-dimethylaniline,$NADPH_2$:oxygen oxidoreductase (*N*-oxide-forming)

Comments: A flavoprotein. Acts on various dialkylarylamines.

Links to other databases: BRENDA, EXPASY, KEGG, WIT, CAS registry number: 37256-73-8

References:

1. Ziegler, D.M. and Pettit, F.H. Microsomal oxidases. I. The isolation and dialkylarylamine oxygenase activity of pork liver microsomes. *Biochemistry* 5 (1966) 2932-2938. [Medline UI: 67122902]

[EC 1.14.13.8 created 1972]

Return to EC 1.14.13 home page
Return to EC 1.14 home page
Return to EC 1 home page
Return to Enzymes home page
Return to IUBMB Biochemical Nomenclature home page

FMO-III not found

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	29	flavin with monooxygenase	USPAT; EPO; JPO; DERWENT	2002/02/21 15:03
2	L6	13	l1 and liver and human	USPAT; EPO; JPO; DERWENT	2002/02/21 15:03
3	L11	698	monooxygenase	USPAT; EPO; JPO; DERWENT	2002/02/21 15:04
4	L16	167	l11 and liver	USPAT; EPO; JPO; DERWENT	2002/02/21 15:04
5	L21	116	l16 and human	USPAT; EPO; JPO; DERWENT	2002/02/21 15:04
6	L26	103	l21 and type	USPAT; EPO; JPO; DERWENT	2002/02/21 15:06
7	L31	75	l21 and ("3" or III)	USPAT; EPO; JPO; DERWENT	2002/02/21 15:06
8	L36	0	l21 and (type with "3")	USPAT; EPO; JPO; DERWENT	2002/02/21 15:07
9	L41	14	l21 and (type with III)	USPAT; EPO; JPO; DERWENT	2002/02/21 15:07
10	L46	3	fmo3 or fmo-3 or fmo-III or fmoIII	USPAT; EPO; JPO; DERWENT	2002/02/21 15:15